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THE ANTIRACHITIC POTENCY OF ERGOSTEROL ACTIVATED BY LOW VELOCITY ELECTRONS

A CLINICAL EVALUATION

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THE following report deals with clinical tests on the antirachitic potency of ergosterol activated by means of low velocity electrons. Of the four previously described methods of converting inactive ergosterol into vitamin D, ultraviolet irradiation alone has thus far proved to be of practical value.[1] Cathode rays[2] and radium emanations[3] have also been shown to be capable of activating ergosterol. Up to the present time, however, these two procedures have not been found to be utilizable on a commercial scale. Bills[2] succeeded in demonstrating that certain sterols can be endowed with antirachitic properties by chemical means, but this procedure is too complicated for practical use and so is of theoretical interest only. The low velocity electron process is an entirely new method for activating ergosterol. Like the ultraviolet ray process, it can be employed on as large a scale as may be desired. We are convinced that it represents a fundamental contribution to our knowledge of vitamin D and thus merits the critical clinical study reported here.

Since numerous bioassays had already demonstrated the antirachitic value of this new ergosterol preparation in the case of the rat, our primary purpose in carrying out the present investigation was to determine whether or not it is capable of curing and preventing rickets in the human subject. A secondary objective was to obtain some information regarding the preventive dosage required by infants.

MATERIALS AND METHODS USED

A detailed description of the technic involved in preparing the antirachitic material used in our study is beyond the scope of the present

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paper. The research staff of the General Mills, Inc., which manufactures this product,* kindly supplied us with a brief description of the process. The basic raw material used is highly purified, crystalline ergosterol. The method of activation is fundamentally different from the ordinary photochemical method that employs ultraviolet radiant energy. In the latter process, energy necessary for causing the transformation of ergosterol into an antirachitic substance is absorbed from sources of ultraviolet radiant energy having a well-defined frequency between certain critical limits. It has been found that the energy for this purpose can be obtained also from low velocity electrons. In this process the electrons are caused to impinge on the ergosterol molecule, and under proper conditions the resulting exchange of energy causes the conversion of the ergosterol molecule to vitamin D. Due to the highly technical character of the process the initial activation, the subsequent purification, and for convenience of distribution the final addition of the product to a suitable vehicle, such as a vegetable oil, are all carried out under the constant supervision of a scientifically trained personnel. Clear bland oil solutions of the vitamin are prepared in concentrated form, and after bioassay, are adjusted to the desired potency by dilution with oil. Such oil solutions are then sent to accredited commercial or university laboratories for bioassay in accordance with the U.S.P. XI method.

Three different stock solutions of the vitamin D material were tested by us in three separate series of experiments carried out between January, 1934, and June, 1936. All of these and the single lot of high grade cod liver oil, which was used in a control series of cases, were subjected to rat assay by the U.S.P. method before, near the middle, and again toward the end of the period covered by our clinical experiments. Results of the various assays were consistent and showed the potency to remain practically unchanged during this period.

The stock solution supplied to us for our original test study contained 12,000 Steenbock units (32,400 U.S.P. or international units) per gram. That for the second series of experiments contained 18,000 Steenbock units (48,600 U.S.P. or international units) per gram. For ease and accuracy in dispensing, these samples were diluted by us with sesame oil, which had previously been found by rat assay to be devoid of antirachitic activity. Such dilutions were made by accurately weighing out a given quantity of stock solution and making the same up to such a volume that the desired daily dose could be obtained in a volume of 1 c.c. or less at room temperature. The vitamin preparation used in the third series of tests (1935-1936) was supplied in a concentration of 600 U.S.P. units per gram, making dilutions by ourselves unnecessary.

Both curative and preventive tests were carried out. For the *curative* phase of the study seven artificially fed infants, shown by clinical and

*The process is controlled by American Research Products, Inc., a subsidiary of General Mills, Inc.

x-ray examinations and blood calcium and phosphorus determinations to have active rickets of varying degrees of severity, were placed in the University of Minnesota Hospital on diets adequate to meet all nutritional requirements except for a lack of vitamin D. The test material was then given as a supplement by means of individual medicine droppers calibrated to deliver the desired dose on the back of the infant's tongue. An additional patient was treated in the out-patient department under similar conditions. The dosages given ranged between 600 and 8,100 U.S.P. vitamin D units daily. Exposure to the direct rays of the sun or to "sky shine" was entirely excluded in all cases. The antirachitic efficacy of the test substance was determined by frequent clinical and x-ray examinations and by changes in the calcium and inorganic phosphorus content of the blood serum.

For the *preventive* tests adequate data were obtained on a total of 106 artificially fed infants. As control subjects twenty-six additional infants of similar age and racial composition and with the same type of basic diet were given preventive doses of standardized cod liver oil instead of our test material. Because of the possible hazard involved in allowing the development of rickets, control studies on untreated infants were not included. However, other observers[5] have adequately demonstrated that rickets of mild, moderate, and even severe grades occurs in a relatively high percentage of infants who are given diets similar to that used in our studies but who are deprived of vitamin D and direct exposure to ultraviolet rays. Nearly one-half of the subjects tested in our series were classified as premature infants on the basis of weight and length at birth. Practically all of the babies available for the study were members of the more lightly pigmented branches of the white race. The great majority of the infants included in the investigation were born at the Minneapolis General Hospital, the University of Minnesota Hospital, or at one of the several well-conducted community homes for mothers of illegitimate babies in Minneapolis and St. Paul. Such infants were usually placed on the test substance before leaving the hospital or when artificial feeding was begun and were then followed up in the well-regulated infant welfare clinics of Minneapolis, which are under the medical supervision of their general director, Dr. E. J. Huenekens, and assisting pediatricians, all of whom hold appointments on the pediatric staff of the University of Minnesota.

The basic diet was essentially the same for all subjects throughout the study, consisting of nonfortified, boiled cow's milk with 5 per cent added sugar. This was given in quantities sufficient to insure normal increases in growth and weight. Orange juice was given in customary amounts throughout the period of observation. Cooked cereal and puréed vegetables were given in increasing amounts after the fifth month of life in most instances. Egg yolk was entirely excluded from the diet and direct exposure of the babies to the sun was avoided so far as pos-

sible. Dosages of the test substance varied in different series of tests between 300 and 1,620 U.S.P. units per day for full-term infants and between 540 and 3,240 U.S.P. units per day for premature infants. In the cod liver oil control tests premature infants were given 600 U.S.P. units per day, whereas full-term infants received either 300 or 450 units. All oil samples were given by means of individual medicine droppers which were calibrated to deliver the dosage desired.

The antirachitic efficacy of the material given was judged by clinical and x-ray examinations at monthly intervals over periods varying between twenty and forty weeks. As an additional check the calcium and inorganic phosphorus of the blood serum were determined at or near the end of the test period. Calcium was determined by the method of Kramer and Tisdall,[6] as modified by Clark and Collip,[7] and the inorganic phosphorus by the procedure of Kuttner and Lichtenstein.[8] Tests were carried out with a few exceptions during the autumn, winter, and spring months only. The exceptionally long and cold winters of Minnesota tend to exclude the interfering factor of exposure to the sun's rays. The roentgenograms of the forearm were nearly all made at the University of Minnesota Hospital with a uniform technic similar to that recommended by Eliot.[9]

The only important respect in which our general procedure has fallen short of that proposed by Eliot and Powers[10] in making clinical tests for the antirachitic potency of vitamin D fortified milks was our unavoidable failure to include a certain minimum percentage of infants of the highly pigmented races. According to the most recent investigation on the subject by Eliot and her coworkers,[11] however, colored infants receiving the same dosage of antirachitic vitamin as white infants showed less tendency than the latter to develop rickets during the winter months, that is, when the factor of sunlight was not involved. Because of the unavailability of colored subjects, we chose to include as many prematurely born infants as possible in our tests because of the well-known increased tendency for such babies to develop rickets. Since none of the subjects included in the preventive tests had ever received any antirachitic substance or ultraviolet light treatments before our experiments were begun, it will be recognized that the greater the age at which administration of the test substance was begun, the more severe was the test. However, in the great majority of instances the subjects were given the test material from the first two or three weeks of life on.

RESULTS

For the sake of brevity, samples of representative data from both curative and preventive studies are presented in the following series of tabulated summaries. In addition, photographs of serial x-ray films are reproduced in some of the curative cases. Space does not permit repro-

duction of the large series of almost uniformly negative roentgenograms obtained in the preventive tests. Throughout the entire report dosages of the test substance and of cod liver oil are expressed exclusively in terms of U.S.P. vitamin D units.

Curative Tests

Examination of the data summarized in Table I shows that the eight infants selected for the curative tests were all suffering from active rickets when such tests were begun, as indicated by clinical findings, x-ray diagnosis, and serum phosphorus and calcium values. While we recognize the desirability of a preliminary control period before beginning specific therapy, the extra risk involved in allowing the patient to go without treatment was considered to be unwarranted in the particular cases included in this study because they had not recently been exposed to ultraviolet rays, they had not been given vitamin D in any form, and their previous diets were not sufficiently unlike the basic diets used throughout the study to justify postponement of remedial therapy. The only patient who had received vitamin D previously was L. P., a rapidly growing premature infant, who had been a subject of one of our preventive experiments. After being transferred at the age of six weeks from the hospital in which he was born to a community home for illegitimate infants, his supervision was so modified that the amount of special oil given over the following two months could not be ascertained. We have some reason to believe that he received very little or none during his stay in the second institution.

The daily dosage of test material given to the first five infants listed in Table I now appears to be unnecessarily large. This excessive dosage is accounted for by the fact that we were laboring under the false impression extant at the time that the effective dosage of activated erogosterol was many times that of ordinary antirachitic vitamin from animal sources. A comparison of the antirachitic effects produced by these larger doses with those resulting from the smaller, however, reveals no advantage in favor of the former. So far as this rough evaluation can be relied upon, it would appear that the smaller dosages (600 to 3,000 units) were of sufficient size to produce the maximum response.

Reference to the column on chemical data shows that the serum calcium and inorganic phosphorus were both at levels above the recognized lower limits of normal by the end of the third week of treatment or earlier. X-ray examinations likewise revealed definite evidence of healing rickets by the end of the second or middle of the third week of the test. Clinical improvement manifested itself even before the routine blood and x-ray examinations were made. In the two cases showing evidence of infantile tetany, all symptoms of this condition had disappeared by the end of the second week of the test. It will be noted

TABLE I

SUMMARY OF DATA ON CURATIVE TESTS—ACTIVATED ERGOSTEROL

CASE	DATE	BODY WT. IN KG.	DAILY DOSAGE OF TEST SUBSTANCE; DATE BEGUN	CHEMICAL DATA ON SERUM MG./100 C.C.			X-RAY DIAGNOSIS	CLINICAL FINDINGS
	1934			*Ca*	*P*	*Ca × P*		
1. V. B. Male; wht. Age, 9 mo. Birth wt. 3.77 kg.	2/ 1	9.90	8,100 2/3/34	7.9	3.3	25	Active rickets, moderately severe	Enlargement of wrists; head sweating
	2/12	9.95		10.9	4.6	50		
	2/21	10.20		10.8	6.4	68	Healing well advanced	No head sweating
	3/ 6	10.45		9.7	5.5	53	Healing almost complete	Markedly improved
2. J. W. Female; wht. Age, 18 mo. Birth wt. 4.11 kg.	4/14	10.85	8,100 4/15/34	8.7	2.4	21	Active rickets, severe	Prominent costochondral junctions; parietal bossing; enlarged wrists; anemia
	5/ 9	11.11		10.8	7.4	80	Marked healing	
	5/23	11.00		11.0	6.5	71	Marked healing	Improved
	6/ 9	11.34		–	–	–	Healing complete	General condition satisfactory
3. D. M. K. Female; wht. Age, 7 mo. Birth wt. 2.73 kg.	4/13	8.14	8,100 4/15/34	10.1	2.8	28	Marked osteoporosis; cupping and fraying of end of ulna	Prominent wrists and bosses
	4/27	?		Not permitted			Beginning healing	Tissues less flabby; color good
	5/11	8.69		Not permitted			Healing advanced but incomplete	Condition satisfactory
4. J. W. Female; wht. Age, 7.5 mo. Birth wt. 3.18 kg.	2/13	7.54	8,100 2/14/34	8.0	1.9	15	Active rickets, severe	Wrists and costochondral junctions enlarged; craniotabes; anemia
	2/21	7.78		9.9	3.2	32		
	3/ 6	7.92		10.5	4.4	46	Marked healing	Much improved
	4/13	8.10		10.8	6.5	70	Healing complete	Condition essentially normal

TABLE I—CONT'D

CASE	DATE	BODY WT. IN KG.	DAILY DOSAGE OF TEST SUBSTANCE; DATE BEGUN	CHEMICAL DATA ON SERUM MG./100 C.C.			X-RAY DIAGNOSIS	CLINICAL FINDINGS
5. B. G. Female; wht. Age, 11 mo. Birth wt. 1.82 kg.	3/13	6.42	8,100 3/14/34	8.5	2.4	20	Active rickets, very marked	Head sweating; marked enlargement of bosses; wrists and costochondral junctions; delayed physical development; anemia
	3/28	6.53		11.3	5.0	56	Healing rickets	
	4/13	6.81		10.7	5.4	58	More advanced healing	Much improved
	5/ 9	7.30		10.6	7.0	74	Healing complete	Condition satisfactory
6. B. B. Female; wht. Age, 4 mo. Birth wt. 2.42 kg.	4/ 2	4.71	3,000 4/3/35	9.3	3.3	31	Active rickets, moderately severe	Beading of ribs; craniotabes; anemia; head sweating
	4/21	5.25		10.6	5.3	56	Healing rickets	Marked improvement
	5/ 6	5.90		9.8	5.8	57	Healing complete	Condition satisfactory
7. L. P. Male; wht. Age, 3 mo. Birth wt. 1.55 kg.	9/29	2.82	1,200 10/1/34	6.0	3.7	22	Active rickets, extremely severe; marked osteoporosis	Convulsions and other signs of tetany; craniotabes
	11/ 9	4.18		9.6	5.6	54	Healing rickets	
	11/23	4.64		10.7	6.5	69	Healing complete	Marked improvement
	1936							
8. S. N. Male; wht. Age, 10 mo. Birth wt. 3.06 kg.	4/28	8.02	600 7/30/36	8.4	3.1	26	Active rickets, moderately severe	Mild craniotabes; tetany with convulsions; marked sweating; parietal bossing
	5/12	8.50		9.4	3.6	36	Beginning healing	No signs of tetany or sweating
	5/21	8.50		9.8	5.9	58	Healing rickets, fairly advanced	General condition much improved
	6/11	8.60		10.2	5.9	60	Healing complete	Condition satisfactory

Fig. 1.—Case 2 (J. W.). *A*, x-ray of forearm and wrist on April 14. Severe active rickets. *B*, x-ray on May 9 after three weeks of treatment. Marked healing. *C*, x-ray on May 23. Healing still further advanced.

that healing was complete in all cases except two, in which it was greatly advanced by the end of the period of observation. It may be observed, also, that healing of the rickets took place in the presence of a satisfactory gain in weight in most instances. In no case was there a net loss in body weight.

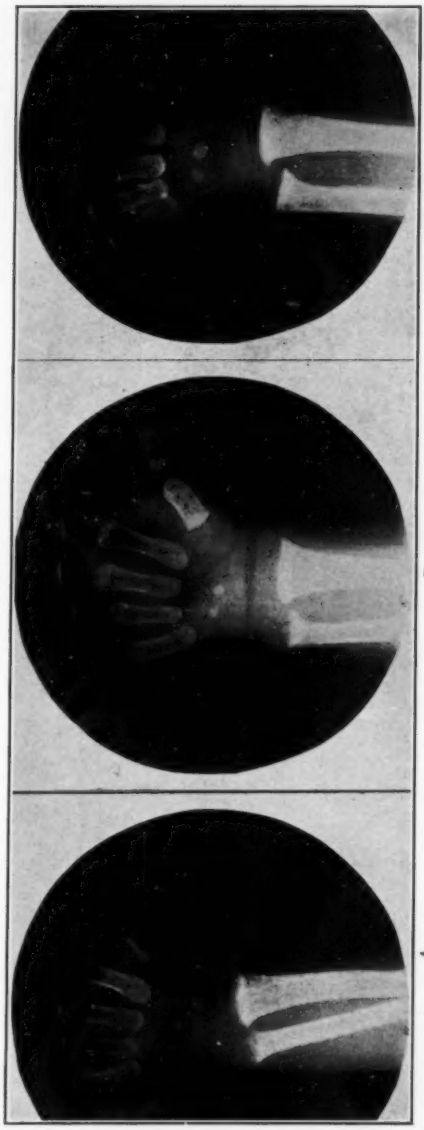

Fig. 2.—Case 4 (J. W.). *A*, x-ray of forearm and wrist bones on February 13. Severe active rickets. *B*, x-ray of same on March 6. Marked healing of rickets after three weeks of treatment. *C*, x-ray on April 13. Healing of rickets complete at end of eight weeks.

Figure 1 shows the x-ray evidence of rickets in the arm and wrist bones of J. W. (Case 2) before introduction of the test substance and again at intervals afterward. The marked fraying and cupping of the distal ends of the ulna and radius are evident in the first picture. By the end of the third week after the activated ergosterol was first given, the x-ray appearance of the bones was that shown in the second picture.

It is obvious that healing was already fairly advanced, although not complete. The third picture of the series, taken almost two weeks later, shows the bones to be still more dense but not yet completely healed.

FIG. 3.—Case 6 (B. G.). *A*, x-ray of right wrist and forearm on March 13. Active rickets of marked severity. *B*, x-ray of same region on March 28. Healing rickets apparent after two weeks of treatment. *C*, x-ray of same wrist on April 13, one month after beginning of treatment. Healing of rickets still more advanced. *D*, x-ray of May 9 after seven weeks of therapy. Rickets healed.

A fourth roentgenogram taken seven weeks after treatment was begun showed what was interpreted as being complete healing, the distal ends of the arm bones showing no cupping or irregularities. Unfortunately this particular film was misplaced before a photographic reproduction was obtained.

The roentgenograms of J. W. (Case 4) obtained before, three weeks after, and 8 weeks after administration of the test substance was be-

Fig. 4.—Case 7 (L. P.). *A*, x-ray of forearm on September 29. Extreme degree of active rickets. *B*, x-ray of same forearm on November 9, five weeks after treatment was begun. Marked healing of rickets. *C*, x-ray of forearm on November 23 after seven weeks of treatment. Healing of rickets essentially complete.

gun are reproduced in Fig. 2. The first film shows very pronounced cupping and fraying of the distal ends of the ulna and radius with a moderate degree of rarefaction of the shaft. The second picture of

the series shows a definite increase in the degree of calcification and a striking decrease in the irregularity previously present at the ends of the bones. After eight weeks of treatment healing was complete, as shown in the final film of the series.

The four roentgenograms reproduced in Fig. 3 were obtained in the case of B. G., the most severely rachitic infant of the series. The first, which was taken before administration of the test substance was begun, shows fairly marked rarefaction of all of the bones and extremely pronounced cupping and fraying of the distal ends of both ulna and radius. In the second picture, obtained two weeks following institution of the antirachitic therapy, the evidence of healing is very pronounced, particularly at the ends of the long bones. The film taken at the end of the fourth week shows the healing process to have advanced still further. At the end of seven weeks of treatment healing appeared to be essentially complete.

Roentgenograms of L. P. (Case 7) are reproduced in Fig. 4. The patient was a very small premature infant kept in the hospital in which he was born for the first six weeks of life. There he received 270 units of the test substance daily for one month, after which he was transferred to the nursery of a community home for illegitimate infants. While it was presumed that a supply of the special test oil would be sent with the patient at the time of his transfer, subsequent inquiry left the impression that he probably failed to receive the prescribed dose, if indeed he received any of the antirachitic substance. At the age of fourteen weeks the clinical diagnosis of rickets with tetany was made. This was confirmed roentgenographically and by serum calcium and phosphorus determinations.

The first film shows an extreme degree of osteoporosis with marked cupping and fraying of the distal ends of the ulna and radius and subperiosteal rarefaction of all of the bones. Five weeks after administration of the test substance was begun in doses of 1,200 units daily, the second film reproduced here was obtained. This shows healing of the rickets to be well advanced, although rarefaction and cupping are still in evidence. After seven weeks of treatment healing appeared to be complete, as shown in the third picture.

Preventive Tests

The preventive tests on the antirachitic efficacy of ergosterol activated by the low speed electron process were carried out in three distinct series. These were made in different years with different lots of the test substance and with dosages at different levels. Since the source of untreated ergosterol and the technic of activation remained essentially unchanged, there is no reason to believe that the vitamin D preparations used in the different series differed qualitatively. Therefore, the three series of tests made in different years may be considered together

as a single study. The cod liver oil tests made in connection with series 3 serve as a control series for the entire study even though the dosages were confined to the lower range.

With a few exceptions all infants included in the study were examined at monthly intervals by members of our own group, either in the Infant Welfare Clinics of Minneapolis or in the maternity homes or hospitals where they were born. To avoid errors in the administration of the oil and to secure cooperation as regards diet and the avoidance of exposure to sunlight, explicit written as well as verbal directions were given to the nurse or mother of each infant included in the study. These were rechecked with the mothers at monthly intervals on their return visits to the well baby clinics. Home visits were made by the Visiting Nurses' organization when found necessary.

The kinds of data obtained are indicated in the column headings shown in Tables II and III, which summarize the results obtained from the third series of experimental subjects and the cod liver oil control series, respectively. For lack of space, detailed tabulations of the data from the first and second series were omitted. Inasmuch as the results were essentially the same for the three series of cases, the samples presented in Table II are truly representative.

Since rapid bone growth tends to favor the occurrence of rickets and cessation of growth or loss of weight to inhibit its development, the infant's weight and total body length were determined at the time of each visit as a check on this factor. Crown-heel length was measured by means of accurately constructed measuring boards. All but a few of the x-ray films were obtained with a uniform technic by a single technical assistant and were regularly interpreted by one of us (L. G. R.) and independently examined by the others as well. Whenever a question arose in connection with the x-ray reading in regard to the possibility of very slight rickets being present, the infant's blood serum calcium and inorganic phosphorus were determined, and the roentgenogram was repeated as a check on our interpretation. The clinical examiners attempted to lay stress on such factors as general nutritional state, the behavior, and the body development, as well as on the commonly recognized accompaniments of active rickets, such as head sweating, flabbiness of muscles, anemia, central craniotabes, and enlargement of the wrists, costochondral junctions, and cranial bosses. The possible influence of complicating diseases was also recognized. Serum calcium and phosphorus determinations were made at or near the end of the period of examination in the case of each infant. Blood samples were taken, therefore, during the winter months or in May or early June, when the great majority of test infants were between twenty-four and thirty-two weeks of age.

In our first series of clinical tests, twenty-three full-term and twelve premature infants met the full requirements of the study, remaining

under observation between five and seven months. The dosages of the activated ergosterol (1,620 to 3,240 U.S.P. units daily) were deliberately placed at a high level at the outset of our study because these were the first tests made on the human subject with this material and at the time of their initiation we were still laboring under the false impression that the required preventive dosage of viosterol was far above that of vitamin D from other sources. Because of their greater tendency to develop rickets, the premature infants were allowed double the dose given to the full-term infants. The tests were begun in the early days of January, 1934, and were carried through May. Most of the subjects of the study were given the test substance from the first month of life on. Nine of them, however, were between eight and twenty-two weeks of age before they began to receive it. Since none of the latter group had ever received cod liver oil or other antirachitic material and only three were sufficiently old to have been exposed to the sunshine of the preceding summer, this small group of infants subjected the material to a particularly severe test. None of the thirty-five infants developed rickets as judged by clinical, x-ray, or blood chemical evidence. Weight gains of all of the infants were entirely normal throughout the period of observation. Blood samples taken at the end of this time showed the serum calcium to range from 10.4 to 12.1 mg. per 100 c.c. and the serum phosphorus to vary between 5.4 and 6.8 mg. per 100 c.c. There was no essential difference between the results for the full-term and the premature infants.

The second series of preventive tests was begun in the late summer of 1934 and was carried through the early spring months of 1935. Its chief object was to determine the protective value of smaller doses of the test substance. Full-term infants were given 400 and premature infants, 540 units per day.

Because of the great likelihood that most babies born in the summer time would be exposed to sunshine and so would be unsuitable subjects for the test, only those infants in custodial institutions, where special provision for direct exposure to sunshine or "sky shine" did not exist, could be included. This naturally placed a very sharp limit on the number of artifically fed infants that were found to meet our requirements. Sixteen full-term and fourteen premature babies were included. Special care was taken to avoid exposure to direct solar radiations, particularly during July, August, and September. Thereafter, such precaution was practically unnecessary because of the onset of very cool or cold weather. With a few exceptions, the premature infants were kept in the secluded special nurseries of the hospitals in which they were born until they were three months of age, and monthly roentgenograms were taken there. That rickets can develop in any part of the world and in any season, if infants are protected from the direct or reflected rays of the sun and are not given vitamin D, is now generally recognized. This was demonstrated

very clearly as regards the late summer and early autumn season in the case of one of the small but rapidly growing premature infants (L. P.) in the present series, who developed severe rickets with tetany under the conditions of our experiment.

A survey of the data obtained from this series of cases shows that none of the full-term infants and but the one of the premature infants, receiving 400 and 540 U.S.P. units of the test substance, respectively, developed rickets that could be diagnosed by clinical, x-ray, and blood chemical findings. Serum calcium values varied between 9.8 and 12 mg. per 100 c.c., while the phosphorus ranged from 5.4 to 7.2 mg. per 100 c.c. Weight gains were equal to or slightly above the normal expected gain for this age period. The average weekly gain in length was 0.67 cm. for infants measuring between 53 and 58 cm. in length at the beginning of the test and 0.72 cm. for those with beginning lengths between 42 and 49 cm.

The single infant which developed rickets during the months of August and September is known with certainty to have received but 270 units of the vitamin D preparation daily between July 12 and August 15. While it was intended that he should continue to receive it after transfer in August from the hospital of his birth to another institution, attendants at the latter were unable to say at a later time, when tetany manifested itself on September 28, whether or not he had done so. Our impression is that he received little or none during the six weeks prior to his being transferred to the University of Minnesota Hospital to serve as a test subject in the curative phase of our study (see Table I). Unfortunately no x-ray other than the initial one taken at the age of two weeks was obtained in this particular case until severe rickets had developed.

Eighteen full-term and twenty-two premature infants were included in the third series of preventive tests, most of which were carried out between the middle of September, 1935, and the latter part of May, 1936. Some were extended to the early part of June to lengthen the period of observation. The same general precautions and requirements adopted for the previous series were maintained throughout this phase of the study. In fact the regularity of examination and the home control of the infants were perhaps more nearly ideal in this than in the previous series because of the improvement in our organization and technic as a result of experience.

The preventive dose for fourteen of the full-term infants was 300 U.S.P. units, which is the minimum so far tested. For the remaining four full-term infants it was 450 units. All but one of the premature infants were given 600 U.S.P. units daily. The other was given but 300 units.

The pertinent data obtained from this study are presented in Table II. It will be observed that with the exception of one premature infant

TABLE II

SUMMARY OF DATA ON PREVENTIVE TESTS—ACTIVATED ERGOSTEROL. SERIES 3. MONTHLY X-RAY AND PHYSICAL EXAMINATIONS NEGATIVE FOR RICKETS

NAME	DATE OF BIRTH	BIRTH WEIGHT IN KG.	AGE (WEEKS)		WEIGHT (KG.)		LENGTH (CM.)		CHEMICAL DATA ON BLOOD SERUM MG./100 C.C.		
			AT BEGIN. OF TEST	AT END OF TEST	AT BEGIN. OF TEST	AT END OF TEST	AT BEGIN. OF TEST	AT END OF TEST	CA	P	CA × P
Full-Term Infants—Received 300 Units Daily											
R. D.	10/ 9/35	2.79	7	28	3.42	7.35	51	68	11.5	7.0	80
J. G.	10/21/35	3.13	8	26	3.65	7.55	55	70	11.2	6.0	67
J. H.	9/ 8/35	3.32	8	32	5.05	8.16	57	72	11.4	6.5	74
M. H.	11/ 4/35	2.95	4	25	3.35	6.80	53	70	12.6	6.2	77
T. J.	11/15/35	3.39	7	24	4.84	7.43	57	67	11.2	6.9	77
R. J.	9/17/35	4.27	14	32	6.69	8.62	62	70	10.7	6.4	69
R. J.	12/ 9/35	4.12	6	24	5.15	7.92	58	67	10.2	5.9	60
M. K.	9/25/35	3.18	7	32	3.93	9.37	57	71	11.9	6.2	74
H. M.	12/ 1/35	3.73	6	24	4.67	7.61	53	67	10.5	6.7	70
S. L.	10/ 9/35	2.82	4	27	3.54	8.58	52	70	9.6	5.9	57
D. Q.	11/16/35	3.24	4	24	4.24	9.08	56	73	11.2	6.5	73
J. R.	11/22/35	3.01	3	25	3.49	9.40	54	72	11.8	6.2	73
T. E.	1/17/36	2.66	3	20	3.46	8.17	56	66	11.4	6.5	74
R. L.	12/ 7/35	2.46	5	24	2.95	6.59	-	64	10.6	5.8	62
Full-Term Infants—Received 450 Units Daily											
J. B.	10/27/35	3.13	6	27	4.62	9.06	55	71	11.7	6.3	73
E. J.	10/ 3/35	4.06	4	27	5.03	8.51	57	69	11.0	5.6	62
D. S.	10/ 3/35	4.34	5	28	4.34	10.58	55	70	11.4	6.1	70
S. S.	11/28/35	3.25	5	24	3.77	6.61	54	66	11.0	6.6	66

TABLE II—CONT'D

NAME	DATE OF BIRTH	BIRTH WEIGHT IN KG.	AGE (WEEKS)		WEIGHT (KG.)		LENGTH (CM.)		CHEMICAL DATA ON BLOOD SERUM MG./100 C.C.		
			AT BEGIN. OF TEST	AT END OF TEST	AT BEGIN. OF TEST	AT END OF TEST	AT BEGIN. OF TEST	AT END OF TEST	CA	P	CA × P
Premature Infants—Received 600 Units Daily											
E. B.	10/22/35	2.22	2	27	2.36	8.52	47	68	9.0	6.5	59
W. B.	12/14/35	2.34	1	24	2.30	8.35	47	67	12.0	6.7	80
W. B.	12/14/35	2.40	1	24	2.40	7.47	46	65	10.9	5.9	64
D. C.	12/ 9/35	2.16	2	24	2.25	5.92	45	63	11.8	6.3	74
I. C.	12/ 2/35	2.47	1	23	2.61	6.20	48	63	11.7	6.2	72
R. H.	11/10/35	2.22	3	25	2.63	6.00	50	63	11.2	4.8	54
D. H.	10/24/35	2.48	1	26	2.39	7.76	47	64	–	–	–
R. N.	12/27/35	2.30	1	22	2.36	7.45	48	64	11.3	6.4	72
K. N.	10/18/35	2.25	2	28	2.42	8.71	46	69	11.4	6.7	76
C. N.	10/18/35	2.19	2	28	2.29	8.66	47	68	11.6	6.7	78
J. S.	10/ 1/35	1.31	4	29	1.85	6.75	44	63	10.2	6.4	65
D. O.	12/ 8/35	2.35	3	23	2.72	6.24	46	63	12.4	5.9	73
M. R.	11/ 9/35	1.40	1	25	1.56	5.50	40	61	11.9	5.1	61
R. S.	10/10/35	2.14	3	28	2.18	6.60	45	63	10.8	6.5	70
R. S.	10/10/35	1.83	3	28	2.08	6.05	48	63	10.6	5.9	63
E. S.	9/29/35	1.60	5	30	2.29	5.63	46	63	11.9	6.1	72
J. V.	12/ 6/35	1.75	1	23	1.87	6.77	44	65	12.4	6.1	75
D. L.	1/ 2/36	1.80	2	22	1.98	6.60	47	64	12.0	6.2	74
D. B.	1/ 1/36	2.33	1	18	2.30	5.46	46	58	–	–	–
G. B.	2/ 9/36	1.82	3	17	2.00	5.24	43	55	11.2	6.4	72
C. F.	12/ 6/35	2.22	3	24	2.60	6.90	47	65	11.7	6.9	81

(C. F.), who was supposed to receive 600 units of the vitamin D preparation daily, none of the entire series showed any roentgenographic, chemical or clinical evidence of rickets throughout the entire period of observation. This particular infant showed slight cupping and fraying of the distal ends of the ulna and radius with evidence of early healing at the time of the fourth-month x-ray examination. Serum calcium and inorganic phosphorus determinations at the time showed 9.6 and 5.8 mg. per 100 c.c., respectively. A roentgenogram was not obtained for the third month because the patient's appointment was not kept, but reference to the earlier films revealed no evidence of rickets. The finding of serum calcium and phosphorus values within the normal zone at the fourth month did not rule out rickets, because healing of the bone at that time was well under way as indicated by the x-ray film. Since healing was more marked at the time of the subsequent examination and complete at the end of the period of observation at the twenty-fourth week of life without any change in dosage of the test substance, one is led to suspect that the baby may have failed to receive his quota of the same during the first part of the two-month period prior to the time of our discovery of healing rickets.

On first inspection, the calcium-phosphorus products of the serums appear to be unusually high in these babies on activated ergosterol. However, as may be seen by reference to Table III, showing values for the control series on cod liver oil, they cover the same range as the latter. The rates of growth for both the premature and the full-term infants, as indicated by measurements of length and weight, were equal to or above the average for infants of this age range. The average weekly gain in length for infants who measured between 54 and 58 cm. at the beginning of the test was 0.68 cm. and that for infants between 43 and 47 cm. at the beginning was 0.80 cm.

In conjunction with the foregoing series of preventive tests on the antirachitic efficacy of ergosterol activated by means of the low velocity electron process, a control series of infants received identical dosages of a high grade of cod liver oil, which was subjected to the same type of bioassay as the test material. The results of these control tests are summarized in condensed form in Table III. Twenty-two of the twenty-six infants making up the series were full-term and four were premature. Fifteen of the full-term babies received 300 U.S.P. units daily and seven received 450 units, while the premature infants were given 600 units per day. None of these subjects developed rickets as determined by clinical, roentgenographic, or blood chemical examinations. Growth in length and weight was considered to be satisfactory in every case. In this respect, as well as that in regard to the clinical, x-ray, and blood chemical data obtained, there were no significant differences between the control and the experimental series of preventive tests. The

TABLE III

SUMMARY OF DATA ON PREVENTIVE TESTS—COD LIVER OIL. CONTROL SERIES. MONTHLY X-RAY AND PHYSICAL EXAMINATIONS NEGATIVE FOR RICKETS

NAME	DATE OF BIRTH	BIRTH WEIGHT IN KG.	AGE (WEEKS)		WEIGHT (KG.)		LENGTH (CM.)		CHEMICAL DATA ON BLOOD SERUM MG./100 C.C.		
			AT BEGIN. OF TEST	AT END OF TEST	AT BEGIN. OF TEST	AT END OF TEST	AT BEGIN. OF TEST	AT END OF TEST	CA	P	CA × P
Full-Term Infants—Received 300 Units Daily											
W. A.	10/ 3/35	2.99	2	30	3.20	8.35	53	70	11.2	6.6	74
G. A.	8/ 1/35	3.18	10	40	4.99	8.98	58	74	11.3	5.6	63
W. C.	10/ 4/35	2.91	4	30	3.19	8.00	51	72	10.1	6.2	62
D. C.	11/ 3/35	2.84	6	25	4.80	8.98	55	69	11.5	6.2	71
J. C.	10/17/35	3.18	8	28	4.32	6.81	58	70	10.5	5.6	59
M. P.	11/12/35	2.98	8	26	3.81	7.30	50	66	11.4	5.9	62
D. R.	9/24/35	2.63	5	28	3.76	7.31	52	67	11.8	6.3	74
C. R.	9/27/35	2.66	4	30	2.75	7.15	47	62	11.7	6.4	74
T. S.	12/26/35	3.18	6	22	4.02	6.99	54	65	11.4	5.7	65
N. T.	10/ 8/35	3.63	4	28	4.15	7.36	55	68	11.6	6.2	72
J. T.	12/11/35	3.22	4	23	4.20	7.66	56	69	12.0	6.7	80
S. T.	10/ 2/35	3.24	8	30	4.88	8.09	59	70	10.5	6.4	67
Y. T.	11/27/35	3.22	7	24	3.93	6.51	55	66	11.4	6.7	76
D. Y.	10/ 2/35	2.46	12	26	5.97	9.08	51	66	-	-	-
E. H.	1/27/36	3.05	4	17	3.80	6.68	53	64	12.0	5.6	67
Full-Term Infants—Received 450 Units Daily											
V. S.	11/19/35	3.59	8	25	3.99	7.94	55	66	11.6	5.8	67
R. G.	10/27/35	2.80	10	24	4.76	6.84	54	65	12.6	6.2	78
D. F.	12/ 9/35	3.35	4	24	3.80	6.86	53	-	10.9	6.4	70
E. F.	10/12/35	2.77	6	28	2.83	4.91	50	62	10.6	6.2	65
P. B.	1/12/36	3.77	6	23	4.13	6.50	57	67	11.4	6.1	69
M. G.	1/ 1/36	3.76	4	20	4.22	9.43	55	66	10.4	6.4	66
M. S.	1/ 5/36	3.32	4	20	3.82	6.13	51	61	10.6	6.5	69
Premature Infants—Received 600 Units Daily											
M. O.	1/ 7/36	2.46	3	19	3.72	5.90	46	60	11.8	6.2	73
D. H.	2/13/36	2.04	2	16	2.10	5.22	45	56	12.2	6.2	75
R. A.	11/25/35	2.27	2	24	2.29	7.16	45	62	12.4	6.3	78
D. K.	10/ 2/35	1.98	4	30	2.02	7.27	42	65	11.7	6.2	72

average weekly increment in crown-heel length was 0.68 cm. for infants measuring between 54 and 58 cm. at the beginning of the test and 0.83 cm. for the four premature infants.

DISCUSSION

The foregoing results of clinical tests on the antirachitic potency of ergosterol activated by the low velocity electron process demonstrate beyond any reasonable doubt that this material is highly efficacious in both preventing and curing rickets and in favoring general bodily growth and development, as vitamin D from other sources is known to do. The most essential requirements for such tests, as proposed by authorities in the field, have been met so far as we are able to judge them. In our opinion curative experiments offer a more certain and more specific test for the antirachitic activity of an unknown agent than do preventive tests, when such extraneous factors as acute infections and exposure to curative light rays are excluded. In a sense, curative experiments may be said to test an antirachitic substance for its medicinal value, while preventive clinical tests serve for its evaluation as a food or food accessory. The necessity for both types of test is of course recognized by all authorities. A well-controlled curative test on a single rachitic patient is far more significant than a preventive test on a single normal infant, because a fairly high percentage of normal infants may fail to develop active rickets, even if their diets are deficient in vitamin D over a period of five or six months.

Only two of the 106 infants included in the preventive tests developed rickets. These two were premature infants. The smaller, more rapidly growing infant developed severe rickets; the other developed what we would classify as mild rickets. In both instances irregularities in the regimen outlined may have accounted for the appearance of the disease. At any rate both patients were subsequently cured by the test substance, when it was given regularly.

Whether or not extremely mild rickets, as determined alone by minute roentgenographic changes, occurred at certain stages in a small number of our preventive cases we are not prepared to say. We can say with certainty, however, that, with the two exceptions already mentioned, no evidence of rickets, as ordinarily diagnosed, could be found. This point deserves consideration because there is at the moment a difference of opinion on the part of workers in this field concerning the significance of slight but definite degrees of rarefaction and blurring of the finer architecture of the bones, as shown particularly by special refinements in x-ray technic. Some consider these changes as the earliest signs of extremely mild rickets; others regard them merely as accompaniments of excessively rapid bone growth. Other interpretations might also be offered. Until such x-ray changes have been accurately correlated with histologic appearances and

with mineral balance studies, no final interpretation of their meaning can be given. As far as our own study is concerned, we can say merely that such minute alterations were observed at times but just as frequently in the cod liver oil series as among the subjects on the ergosterol preparation. Furthermore, the x-ray films from infants receiving 1,620 units per day were on the average indistinguishable from those obtained in cases receiving 300 units daily. In this large series of normal infants, there appears to be no direct relationship between the degree of calcification of the bone, as shown by x-ray, and the level of blood calcium and inorganic phosphorus. When such minor degrees of rarefaction have been seen during the early months of observation, they have not in our cases gone on to the development of definitely diagnosable rickets in subsequent months, but have usually disappeared or have become less conspicuous without change in dosage of the antirachitic test substance. It is our conviction, therefore, that these minor deviations from the average appearance of the x-ray film do not in all probability indicate the occurrence of rickets. The calcium and inorganic phosphorus of the blood serum were uniformly normal in the preventive tests and frequent clinical examinations revealed no evidence of rickets.

As regards dosage of ergosterol activated by the low velocity electron process, it must be pointed out that the minimum preventive dose for either full-term or premature infants has not as yet been determined. That it is below 300 U.S.P. units per day for the average full-term infant and below 600 units for the premature infant appears certain. The one premature baby, who received but 300 units, did not develop rickets, but this single case does not establish the level for all premature infants. Since as little as 135 units, or even less, of vitamin D from animal sources has recently been found to prevent clinically significant rickets, the minimum preventive dose of activated ergosterol may be of this general magnitude or one and one-half times this, if Jean's estimate[12] is correct. The recent report by Eliot and her coworkers,[11] already referred to, indicates that activated ergosterol is just as effective, rat unit for rat unit, as cod liver oil in preventing infantile rickets.

SUMMARY AND CONCLUSIONS

1. The antirachitic potency of ergosterol activated by low velocity electrons has been determined by curative tests on eight infants with severe or moderately severe rickets and by preventive tests on fifty-eight full-term normal infants and forty-eight premature infants.

2. Control preventive tests were made on twenty-six infants with assayed cod liver oil as the source of vitamin D.

3. Frequent clinical and roentgenographic examinations and serum calcium and inorganic phosphorus determinations were employed as criteria of presence or absence of rickets.

4. Measurements of the infants' weights and lengths showed body growth to be satisfactory during both the control and the experimental preventive tests.

5. Active rickets showed evidence of healing in all cases within from two to three weeks and apparently complete healing by the end of from five to eight weeks of treatment with the test substance, as shown by x-ray changes in the bones and by return to normal of the calcium and inorganic phosphorus of the blood serum.

6. All of the normal infants, who were given the activated ergosterol, were protected against rickets, except two. Known irregularities in the regimens of these two subjects might well account for such failures.

7. The roentgenographic, clinical, chemical, and growth data obtained for the experimental subjects were on the whole indistinguishable from those pertaining to the control subjects receiving cod liver oil.

8. The average minimal preventive dose of ergosterol activated by means of low velocity electrons has not as yet been established. From the results reported here it appears to be not above 300 U.S.P. vitamin D units per day for full-term infants and 540 units per day for premature infants.

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EPILEPSY IN CHILDHOOD

I. A Statistical Study of Clinical Types

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SELECTION OF CASES

A SPECIAL clinic for epileptic children has been in operation at the Harriet Lane Home since January, 1928. It has presented the opportunity to study epilepsy in an unselected group of children outside of institutions and to follow the disease over a period of seven years.* In a series of papers we shall report a clinical analysis of the types of epilepsy encountered, the incidence of remissions, and the results with the ketogenic diet.

In making any clinical study of epilepsy, it is first necessary to state the criteria for the diagnosis. Since it is so difficult to formulate an entirely adequate definition for the symptom-complex of epilepsy, some modern workers have attempted to drop the term and to speak of the "convulsive state." The neurophysiologist does not attempt to draw a sharp distinction between epileptic and febrile convulsions and often includes in his studies the whole "borderland of epilepsy" as described by Gowers.[1] Nevertheless, the term "epilepsy" still implies to the clinician certain types of recurring seizures which should be distinguished from other attacks of apparently less serious import, usually having a tendency to cease. Instead of defining more accurately what we consider epilepsy, it is easier to state what types of cases have been excluded in this study as not epileptic. In the first place, care has been taken to exclude all patients who are subject to hysterical episodes, temper tantrums, breath-holding attacks, and spells of syncope. It is comparatively easy to differentiate such conditions from genuine convulsions, but often long periods of observation are required to distinguish them from minor epileptic attacks. Next, those patients have been excluded who have febrile convulsions, tetany, acute neurologic lesions, syphilis of the central nervous system, or recognizable brain tumor. This leaves a group of patients subject to the generally accepted symptom-complex of epilepsy. Some of them have no recognizable brain lesion; others have associated mental defects; and still others have recognizable brain lesions.

From the Harriet Lane Home of the Johns Hopkins Hospital and the Department of Pediatrics of the Johns Hopkins University School of Medicine. Aided by the support of the Epilepsy Medical Research Fund.

*The careful follow-up of this group of patients has been possible largely through the efforts of a full-time social worker, Miss Mary McCulloch. All the patients have been studied by either Dr. E. M. Bridge, Dr. L. Kajdi, or the author. Psychiatric studies have been made on the majority of the patients by Dr. Leo Kanner and his coworkers.

Of 425 children who have been examined in the Epilepsy Clinic, 115 are not included in this study because the period of observation was not sufficiently long to obtain adequate data. We have accurate information concerning 310 children whose present status is known. In 56 instances, however, the diagnosis of epilepsy was considered erroneous or questionable. The remaining 254 were thought to have epilepsy and are the subject of this study.

CASES IN WHICH THE DIAGNOSIS OF EPILEPSY WAS ERRONEOUS

The 56 patients in whom the diagnosis of epilepsy was considered erroneous or questionable are listed in Table I.

TABLE I

PATIENTS IN WHOM THE DIAGNOSIS IS QUESTIONABLE OR NOT EPILEPSY

A. Attacks definitely convulsions			18
Febrile convulsions	13		
Syphilis	2		
Brain tumor	1		
Obesity (possibly endocrine)	1		
Only one convulsion	1		
	18		
B. Attacks of questionable nature			38
Peculiar behavior in defective children		9	
Questionable episodes in mentally normal children		6	
Syncope		9	
Hysteria		3	
Awkwardness and stumbling in young children		2	
Breath-holding		2	
Frights and night-terrors		2	
Malingering		1	
Unreliable history (possibly epilepsy)		4	
		38	
Total			56

These figures give no indication of the relative frequency of such conditions as compared with epilepsy. Numerous cases of this sort are seen each year in the general pediatric dispensary and are correctly diagnosed. Only the more doubtful ones are referred to the Epilepsy Clinic and any mistake in diagnosis is usually due to the inability to obtain from the child's parents an accurate description of the seizure. In doubtful cases the production of petit mal attacks by means of the hyperventilation test has been of some diagnostic value. However, the failure to induce attacks by hyperventilation does not exclude the possibility of epilepsy. We have not employed the hydration test suggested by McQuarrie and Peeler[2] and by Jacobsen.[3]

When convulsions have occurred only in association with acute febrile episodes, the prognosis is usually good, and the diagnosis of epilepsy should not be made. However, we have seen a number of

children who, after having repeated febrile convulsions over a number of years, later developed typical epileptic attacks unassociated with fever or infections. It is our impression that the frequent occurrence of febrile convulsions especially in defective children may be the forerunner of habitual epilepsy.

CLASSIFICATION OF EPILEPSIES

It is generally recognized that the epilepsies may be due to many different causes and may take many different forms. It would be desirable to classify them on an etiologic basis, but in the present state of our knowledge this is impossible. In the older literature an attempt was made to classify the epilepsies as "essential" or "idiopathic" and "organic" or "symptomatic." Modern studies with encephalography suggest that many cases which would formerly have been regarded as idiopathic show an underlying organic cerebral lesion. It has not been found feasible or advisable to make routine encephalographic studies in the Epilepsy Clinic. Furthermore, the interpretation of encephalograms is frequently open to serious doubt. It is, however, of interest to attempt a clinical classification of the types of epilepsy encountered. One may readily pick out certain cases in which the history or the neurologic findings give definite evidence of an organic brain lesion. Other epileptic patients are encountered who present no neurologic signs and no history of neurologic disease (other than epilepsy) and who are normal intellectually. These children offer no ascertainable evidence of any gross cerebral lesion. There is, however, a third intermediate group of epileptic children who are markedly retarded mentally without demonstrable evidence of neurologic disease. Many of these patients are congenitally feebleminded. In other cases, however, it is impossible from the history or the examination to determine whether the mental retardation is congenital or is a result of deterioration in the course of epilepsy. To avoid the necessity of making this dubious distinction, it seems best to group these retarded epileptics together and to separate them from the epileptics with approximately normal intellect. We have arbitrarily set the intelligence quotient of 80 as the dividing line between the two groups of epileptics who have no definite neurologic evidence of cerebral lesions. The upper group therefore contains only epileptic children of fairly high intelligence. As a matter of fact, of the 111 patients included in this group, 14 children had an I.Q. between 81 and 85, 10 had an I.Q. between 86 and 90, and the remaining 87 had I.Q.'s between 90 and 120. In 21 instances the I.Q. was over 100. In the retarded group of 82 children, the I.Q. was below 70 in 58 instances.

The diagnosis of a neurologic lesion was made on the following basis:

Neurologic signs—usually hemiplegias, or monoplegias		15 patients
Constant localization of convulsions, with or without neurologic signs		35 patients
History indicative of brain lesions, but signs absent		
Definite birth injury	3	
Fractured skull	2	
Transient paralyses	4	
Lead encephalitis	1	
Probable epidemic encephalitis	1	
	11	11 patients
		61 patients

Although this grouping is not exact nor scientifically correct, it is a practical and useful clinical classification of epileptic children and seems superior to the old division into "essential" and "organic" epilepsy.

On the basis described, the 254 patients were classified as follows:

Group I. Epileptics with I.Q. over 80 having no apparent neurologic lesions	111	(43.7%)
Group II. Epileptics with I.Q. below 80 having no apparent neurologic lesions	82	(32.3%)
Group III. Epileptics with definite neurologic lesions	61	(24.0%)
	254	(100%)

It is of interest to compare these three groups in regard to the character of the seizures, the frequency of seizures, and the age of onset.

INCIDENCE OF MENTAL DEFECT

The classification of epileptics into the three groups does not reveal the frequency or severity of mental defects among all epileptic children. Only 189 of the patients have been given standardized intelligence tests. However, in all except 8 of the 65 patients who have not been given standardized tests, there is sufficient information to judge whether the intelligence quotient is above or below 80. Table II gives a comparison of the mental ratings in patients with and without evidence of organic neurologic lesions.

It is seen that 57.5 per cent of the patients without evidence of neurologic lesions had an I.Q. above 80 as compared with 41.5 per cent of the patients with neurologic lesions. It can be stated that among all the epileptic children studied 54 per cent had an intelligence quotient above the level of 80. However, the classification into the three groups which we have discussed in the previous section allows one to pick out those patients who represent the type of so-called "essential epi-

TABLE II

INTELLECTUAL RATING OF ALL EPILEPTIC PATIENTS

I.Q.	100+	90-99	80-89	NOT STANDARDIZED. PROBABLY 80-100	TOTAL OVER 80	70-79	60-69	50-59	LESS THAN 50	NOT STANDARDIZED. PROBABLY LESS THAN 80	TOTAL LESS THAN 80	ALL CASES	% OVER 80
No neurologic lesion	21	34	24	32	111	24	17	15	12	14	82	193	57.5
Neurologic lesion	4	3	8	7	22	8	8	4	7	4	31	53	41.5
Total	25	37	32	39	133	32	25	19	19	18	113	246	54.0

lepsy," that is, patients without serious mental defect and without evidence of neurologic lesions. This is represented by Group I which constituted 43.7 per cent of the series.

Our figures concerning mental defects are not strictly comparable with those of other workers. Many of their statistics are derived from a study of epileptics in institutions. Lennox[4] compiled information concerning about 1,500 noninstitutionalized epileptics of all ages in the practice of various neurologists and stated that 65 per cent were mentally normal, 24 per cent slightly retarded, and 11 per cent definitely deteriorated. However, the estimation of the degree of mental defect was based largely on the subjective impression of the physicians rather than on accurate psychiatric studies. Turner[5] found that among 159 patients of all ages studied, 44 per cent (his Table 27, page 149) belonged to Class A ("bright, active, and intelligent") or Class B ("mental condition good except for some defect in memory").

CHARACTER OF SEIZURES

It has been customary to classify the type of seizures as *grand mal* or *petit mal*. As a matter of fact, every gradation in type is encountered, from the severe generalized convulsion to the momentary lapse in the stream of consciousness characterized by a brief staring expression without any motor manifestations. The term "petit mal" has frequently been used rather loosely to describe all minor attacks which are not actual clonic convulsions. This would include not only the momentary lapses of consciousness, but also seizures with minor motor manifestations, such as stiffening or turning of the body or head, drawing up or stretching of the arms, twitching of the face, grimacing, and puffing or blowing movements of the mouth, and various automatic actions. In this paper the term "petit mal" is used to describe only the momentary lapse of consciousness without motor manifestations; other seizures which do not amount to true convulsions are termed "minor motor attacks." It is true that many patients who are subject to generalized convulsions also have minor seizures either with or without motor involvement. It is also true that in some patients epilepsy first begins with true petit mal attacks; later in the course, minor motor attacks occur, and finally generalized convulsions become manifest. However, some patients are seen who have one type of seizure without ever developing motor manifestations.

In this paper, the patients have been classified in six groups according to the type of seizure: (1) patients having generalized convulsions only, (2) patients having generalized convulsions predominantly with also minor motor or *petit* mal attacks, (3) patients having only "minor motor attacks," (4) patients having constantly localized or jacksonian seizures either with or without loss of consciousness, (5) patients who

have predominantly true petit mal attacks but who have also very occasional convulsions, (6) patients having only true petit mal attacks.

Table III shows the relative incidence of the various types of seizures in each of the three groups of epileptics described.

TABLE III

INCIDENCE OF VARIOUS TYPES OF EPILEPTIC SEIZURES

	EPILEPTICS I.Q. > 80		EPILEPTICS I.Q. < 80		EPILEPTIC NEUROLOGIC LESION		TOTAL	
	NUMBER	%	NUMBER	%	NUMBER	%	NUMBER	%
Generalized convulsions	45	62.2	43	69.5	18	39.3	106	59.0
Generalized convulsions with minor motor or petit mal	24		14		6		44	
Minor motor attacks	19	17.1	20	24.4	2	3.3	41	16.2
Localized convulsions	0	0	0	0	35	57.4	35	13.8
Petit mal with occasional convulsions	8	20.7	4	6.1	0	0	12	11.0
Petit mal only	15		1		0		16 6.3%	
Total	111	100.0	82	100.0	61	100.0	254	100.0

The only type of attack which occurred in 106 patients, or 42 per cent, was the typical generalized convulsion. However, 59 per cent of the patients had predominantly generalized convulsions either alone or combined with occasional minor or petit mal seizures. Among the patients with neurologic lesions, generalized convulsions occurred in 39.3 per cent and localized convulsions either with or without loss of consciousness in 57.4 per cent. (Localized convulsions were accepted as prima facie evidence of a neurologic lesion.) Therefore, the convulsive discharge was the predominant feature in 96.7 per cent of the epileptics with neurologic lesions, 69.5 per cent of those with mental retardation, and 62.2 per cent of the patients with approximately normal mentality.

The infrequency of patients having only petit mal seizures, as we have defined the term, is strikingly shown in Table III. Only 16 such cases, or 6.3 per cent, have been encountered in the entire series of 254. Even when the patients having an occasional convulsion (usually a total of only 3 or 4) are included, there is a total of only 28 cases, or 11 per cent, of the series. Fifteen out of the 16 patients exhibiting typical petit mal attacks exclusively were children of normal mentality. This agrees with the finding of Lennox[4] that patients with petit mal only showed least deterioration. If one considers all cases in which the petit mal type of seizure was the predominant feature of the disease, it is seen that this type of attack was encountered in 20.7 per cent of the group having normal mentality and in 6.1 per cent of the group of retarded children. Typical petit mal was not encountered in any of the patients diagnosed as having neurologic lesions.

Minor motor attacks of the character that we have described occurred in 17.1 per cent of the children with I.Q. above 80 and in 24.4 per cent of the more retarded children. It is probable that in some instances the peculiar actions and mannerisms of severely defective children were mistaken for epileptic seizures, although an effort was made to differentiate and exclude such behaviorisms from the group.

Our figures concerning the relative frequency of the various types of attacks cannot be compared directly with those of other workers because our classification is different. Some of the borderline group of seizures which we have termed "minor motor attacks" would be classified by other writers as grand mal or major attacks and some as petit mal or minor attacks. However, the essential correspondence to our findings is shown by the following figures.

	LENNOX[4]	TURNER[5]	SPRATLING[6]
Grand mal or major types	50%	58.2%	60.0%
Combined types	34%	38.2%	32.0%
Petit mal or minor types alone	9%	3.8%	5.5%
Periods of amnesia	7%	-	-

FREQUENCY OF SEIZURES

We have attempted to study the frequency of seizures in the three different groups of epileptics. Some difficulty attends this because in many cases of epilepsy the frequency varies considerably from time to time. However, when patients have been under observation for long periods of time, one is able to form a fairly accurate estimate of the usual average frequency and can judge, for instance, whether the attacks occur daily to weekly, weekly to monthly, etc. Those cases in which the frequency of seizures has been markedly reduced by treatment are classified in the group to which they belonged before treatment. For example, a patient whose attacks had occurred several times a week before treatment but only once a month after the administration of sedatives is classified as having "daily to weekly" attacks. About one case out of ten defies classification because of the extreme variability in the frequency of seizures. Such cases have been classified as "intermittent types." In 233 cases we have sufficient data on the occurrence of seizures to permit a classification into one of the five following groups:

1. *Daily to weekly*—patients having attacks more frequently than once a week.
2. *Weekly to monthly*—patients having attacks less frequently than once a week but more frequently than once a month.
3. *Monthly to quarterly*—patients having attacks less frequently than once a month but more frequently than once a quarter.
4. *Quarterly to yearly*—patients having attacks quarterly or less frequently.

5. *Intermittent*—patients whose attacks vary so greatly in frequency from time to time that they cannot be classified—for example, the patients whose attacks may occur daily for a long period, then at quarterly intervals and then at weekly intervals.

TABLE IV

FREQUENCY OF SEIZURES—ALL TYPES

GROUP	EPILEPTICS—NORMAL		EPILEPTICS—DEFECTIVE		EPILEPTICS NEUROLOGIC		TOTAL	
	NUMBER	%	NUMBER	%	NUMBER	%	NUMBER	%
Daily to weekly	54	64.0	33	64.2	16	56.7	103	62.3
Weekly to monthly	17		19		18		54	
Monthly to quarterly	12	28.8	9	21.0	13	33.3	34	27.4
Quarterly to yearly	20		8		7		35	
Intermittert frequency	8	7.2	12	14.8	6	10.0	26	10.3
Total	111	100.0	81	100.0	60	100.0	252	100.0

Table IV shows the relative frequency of all types of seizures in the three different groups of epileptic children. It is seen that in 62.3 per cent of the cases attacks occur more frequently than monthly, in 27.4 per cent less frequently than monthly, and in 10.3 per cent they are of intermittent frequency. There is little difference among the three groups of epileptics.

This comparison of the frequency of seizures in the different groups of epileptics does not give a true indication of the severity of the disease because the petit mal and minor types of seizures, which are usually of daily or weekly occurrence, are encountered more commonly in some groups than in others. They are most frequently seen in the children of normal mentality and least frequently in the epileptics with neurologic lesions. To determine the relative severity of the disease in the different groups, it is best to compare the frequency of attacks in those cases in which only convulsions either generalized or localized occur. This has been done in Table V and shows that among the patients with normal mentality convulsions occur more frequently than monthly in 44.4 per cent of the cases, whereas in epileptics with low intelligence or with neurologic lesions the convulsions occur more frequently than monthly in 61 per cent or 62 per cent of

TABLE V

FREQUENCY OF CONVULSIONS, GENERALIZED OR LOCALIZED

	EPILEPTICS I.Q. $>$ 80		EPILEPTICS I.Q. $<$ 80		EPILEPTICS NEUROLOGIC		TOTAL	
	NUMBER	%	NUMBER	%	NUMBER	%	NUMBER	%
More frequent than monthly	20	44.4	25	61.0	31	62.0	76	56.0
Less frequent than monthly	25	55.6	16	39.0	19	38.0	60	44.0
Total	45	100.0	41	100.0	50	100.0	136	100.0

the cases. In other words, more mild cases are encountered among epilepties of normal mentality without neurologic lesions.

AGE OF ONSET

The age at which epilepsy began has been studied in the three different groups. The relative frequency of onset at the various age levels is shown graphically in Chart 1, in which the percentage of the total number of cases of each group has been plotted for each age level. In all three groups of epilepties a larger number of cases begin in the first two years of life than in any similar period. Among the patients having neurologic lesions, a much larger proportion of

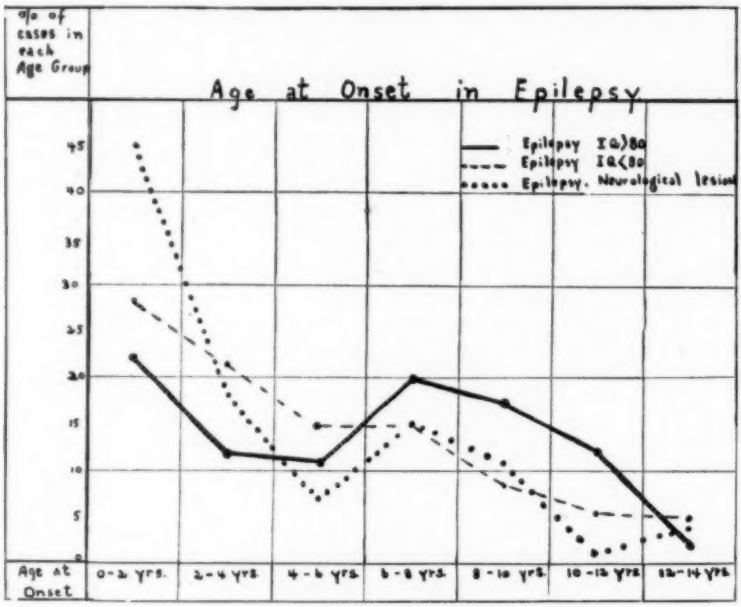

Chart 1.

cases begin in the first two years than in either of the other groups. This is due to the fact that birth injuries or congenital brain defects are responsible for the disease in a comparatively high proportion of these cases. There is a marked decrease in the number of cases beginning between the ages of two years and six years. A distinct increase in the number of cases occurs in the six-to-eight-year period among the epilepties with normal mentality and the epileptics with neurologic lesions, although this increase is not shown in the curve for epilepties with intellectual retardation. After eight years of age all the curves continue to decline. However, our figures probably do not give a correct picture of the relative frequency of onset after the

tenth year of life because the Epilepsy Clinic usually does not accept new patients over twelve years of age. Patients developing the disease after ten years of age are more likely to be seen first in the adult neurologic clinics instead of the children's clinics.

Turner[5] in 1907 studied the age of onset in 1,000 epileptic patients. His curves correspond remarkably with ours except that after the small decline in the incidence in the eighth and ninth years there is another increase in the incidence of the disease, which reaches a second maximum between the ages of twelve and fifteen. From this period onward there is a steady, though not necessarily a progressive, decrease with, however, a slight temporary increase in the number of cases which commence at from twenty-five to twenty-eight years of age.

The relative frequency of onset in the various periods of life is given by a number of authors as follows:

	TURNER[5]	LENNOX[4] 1,500, NONINSTITUTIONAL	CRAIG COLONY[4] 8,151 PATIENTS
Birth to 4 years	17%	15%	32%
5-9 years	14%	13%	18%
10-19 years	28%	36%	33%
20 years and over	41%	37%	17%

SUMMARY

1. Some of the difficulties in making the diagnosis of epilepsy have been discussed. The difficulties usually depend upon incomplete history or observation. So-called "febrile convulsions" are sometimes confused with epilepsy. When seizures are of atypical nature rather than true convulsions, it is sometimes difficult to distinguish them from peculiar behaviorisms exhibited by defective children, syncope, hysteria, and breath-holding attacks.

2. The statistical studies reported here are based upon a group of 254 noninstitutionalized children thought to have epilepsy. All cases with questionable diagnosis were excluded from the group.

3. It is impossible at present to divide epilepsies into an "organic" and an "essential" group. It is probable that many epileptics with severe mental defects have organic cerebral lesions. However, since it is frequently impossible to determine whether a severe mental defect points to a preexisting cerebral malformation causing attacks, or is a result of deterioration following epilepsy, it is thought advisable to subdivide the cases into three groups, as follows:

Group I. Patients with intelligence quotient above 80 and with no evidence of neurologic lesions (43.7 per cent)

Group II. Patients with intelligence quotient below 80 but with no other evidence of neurologic lesions (32.3 per cent)

Group III. Patients with definite evidence of neurologic lesions (24 per cent).

4. Fifty-four per cent of all the patients studied had I.Q.'s above 80; 57.5 per cent of the patients without neurologic lesions were standardized above 80, as compared with 41.5 per cent of the patients with neurologic lesions.

5. The character of the seizures in the three groups of epileptic children is discussed. A distinction is made between true petit mal seizures without motor manifestations and minor motor attacks. The convulsive discharge (either general or localized) was the predominant feature in 96.7 per cent of the epileptics with neurologic lesions, 69.5 per cent of those with mental retardation, and 62.2 per cent of the patients with approximately normal mentality. Only 16 patients, or 6.3 per cent of the entire series, had attacks exclusively of the petit mal type, and 15 of these patients were children of normal mentality. The petit mal attack was the predominant feature in 20.7 per cent of the group with normal mentality and in 6.1 per cent of the group of retarded children. The typical petit mal attack was not encountered in any of the patients diagnosed as having neurologic lesions.

6. A study of the frequency of seizures in the different groups of epileptic children does not give a correct indication of the severity of the disease, due to the fact that petit mal seizures are more common among the children with normal mentality. When the frequency of convulsive attacks is compared in the different groups, it is found that the disease is relatively less severe in the children who have normal mentality. Conversely, mental defects are more often associated with the more severe forms.

7. The age of the onset of epilepsy is discussed. The symptoms are most liable to appear in the first two years of life. There is a decrease in the number of cases commencing between the second and the sixth years and another increase between the sixth and the eighth years. Other workers have shown a third increase in the frequency of onset occurring between the tenth and fifteenth years but this is not indicated by our figures due to the smaller number of children in the older age periods studied by us. The early onset, before the second year, is especially common in children having neurologic lesions since many of these lesions are the result of birth traumas or congenital malformations.

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EPILEPSY IN CHILDHOOD

II. The Incidence of Remissions

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IN JULY, 1935, an effort was made to check up on the condition of as many as possible of the children who had been under treatment in the Epilepsy Clinic of the Harriet Lane Home in order to determine how many were free from attacks.* It was possible to obtain accurate information concerning the condition of 230 children who had been under observation for over one year, that is since July, 1934. Those who had been treated by the ketogenic diet or by intensive dehydration regimes were excluded from the group and will be discussed in another paper. There remained a series of 200 children, some of whom had been treated by the usual sedative drugs, while others had received no treatment at all.

Number and Duration of Remissions

It was found that 46 of the 200 children who had been under observation for more than one year had been free from attacks for the past year or longer. That many of these patients had been free from attacks for continuous periods much longer than one year is shown in Table I.

Table I

Duration of Remissions

Free from attacks for 1 year or longer	46 patients
Free from attacks for 2 years or longer	38 patients
Free from attacks for 3 years or longer	27 patients
Free from attacks for 4 years or longer	21 patients
Free from attacks for 5 years or longer	15 patients
Free from attacks for 6 years or longer	6 patients
Free from attacks for 7 years or longer	5 patients
Free from attacks for 10 years or longer	2 patients
Free from attacks for 12 years or longer	1 patient

It is thus seen that periods of remission lasting one year or longer were encountered in 46 patients, or 23 per cent of the entire group and that remissions lasting two years or more were encountered in at least 19 per cent of the group. However, the period of observation of the entire series has not been of sufficient duration to determine what proportion of patients eventually may have longer periods of freedom.

From the Harriet Lane Home of the Johns Hopkins Hospital and the Department of Pediatrics of the Johns Hopkins University School of Medicine. Aided by the support of the Epilepsy Medical Research Fund.

*The careful follow-up of this group of patients has been possible largely through the efforts of a full-time social worker, Miss Mary McCulloch.

As such a group of epileptic patients is followed from year to year, some of those, who are now free from attacks, may again become subject to seizures; while other patients, who are now showing no improvement, may later become free. This is illustrated by a review of the histories of 35 patients who were found to be free from attacks for over one year at the time a similar study was made in July, 1933. Of these 35 patients, 8 have now had relapses, and 27 have remained free from attacks and are included in the present series as being free for three years or longer. In the past two years 11 more patients have completed a period of freedom greater than two years; and 8, a period of one to two years.

TYPE OF TREATMENT EMPLOYED

There was no uniformity in the plan of treatment. The various sedative drugs were administered in different doses according to what seemed to be the individual needs of the patient. When one drug seemed to have no effect, another was tried. Although an effort was made to keep the patients on continuous treatment, they frequently failed to cooperate and took medication irregularly. Remissions were encountered in some patients who were receiving no therapy, either because their attacks were infrequent, or because they had failed to cooperate, or because they had experienced no benefit from drugs and had insisted on discontinuing them. The type of treatment that was being received at the time the remission occurred is recorded in Table II.

TABLE II

TYPE OF TREATMENT AT TIME OF REMISSION

Phenobarbital	19 patients
Phenobarbital and potassium borotartrate	5 patients
Bromides	7 patients
Bromides and phenobarbital	6 patients
No treatment	9 patients
	46 patients

Of the 37 patients who were receiving sedatives, 29 have been able to discontinue all drugs without relapse, and 26 have had no treatment for over a year. These facts are shown in Table III.

TABLE III

PRESENT PERIOD OF FREEDOM FROM ATTACKS WITHOUT TREATMENT

Still receiving treatment	8 patients
No treatment for 1-6 months	2 patients
No treatment for 6-12 months	1 patient
No treatment for 1-2 years	9 patients
No treatment for 2-3 years	8 patients
No treatment for 3-4 years	1 patient
No treatment for over 5 years	8 patients
	37 patients
No treatment at time of remission	9 patients
	46 patients

It is generally considered advisable to continue treatment for at least two years after attacks have stopped and then to discontinue it gradually. In reviewing our cases in which remissions had occurred, it was found that in many instances the patients had stopped all medication abruptly shortly after the cessation of attacks. This is shown in Table IV.

TABLE IV

LENGTH OF TIME TREATMENT WAS CONTINUED AFTER ATTACKS STOPPED

No treatment at time of remission	9 patients
Less than 1 month after remission	9 patients
1-6 months after remission	7 patients
6-12 months after remission	2 patients
1-2 years after remission	2 patients
2-3 years after remission	5 patients
More than 3 years after remission	1 patient
Not known	3 patients
Treatment still continued	8 patients
	46 patients

The differences in the response to treatment and the difficulties in determining whether the therapy was directly responsible for the cessation of attacks will be discussed in a later section of this paper.

RELATION OF REMISSIONS TO THE TYPE OF EPILEPSY AND THE CHARACTER OF THE SEIZURE

Table V shows the relation of remissions to the various groups of epileptic children and the different kinds of seizures. The classification followed has been discussed in a previous paper.[1] Under each category the upper numeral indicates the number of remissions encountered and the lower numeral the total number of cases in the series. The incidence of remissions for each category is expressed in percentage.

It is seen that remissions occurred in approximately 30 per cent of the children who had an I.Q. above 80 and no evidence of neurologic lesions, whereas they were encountered in about 20 per cent of the cases associated with mental defect or with neurologic lesions. It is possible that the higher proportion of mild cases (i.e., patients with infrequent seizures) in the former group may account for the more favorable prognosis.

The prognosis for remissions appears twice as favorable in patients having attacks of generalized convulsions (23.3 per cent), localized convulsions (25 per cent), or minor motor seizures (25 per cent), as in those whose attacks are predominantly of the true petit mal type (12.5 per cent). However, the total number of patients having the petit mal type of epilepsy is relatively so small that a comparison with the other group is not valid statistically.

RELATION OF REMISSIONS TO THE FREQUENCY OF SEIZURES

The incidence of remissions was studied in relation to the frequency of seizures. It was found that there was no significant difference in

TABLE V

RELATION OF REMISSION TO TYPE OF EPILEPSY AND CHARACTER OF SEIZURE

	GRAND MAL ONLY	GRAND MAL AND MINOR	MINOR ATTACKS	LOCALIZED CONVULSIONS	PETIT MAL WITH GRAND MAL	PETIT MAL ONLY	TOTAL
Group I	13*/35 = 37.1%	3/15 = 20.0%	4/12 = 33.3%	0 = 0	0/2 = 0	2/9 = 22.2%	22/73 = 30.1%
Group II	7/39 = 18.1%	3/14 = 21.4%	4/18 = 22.2%		0/4 = 0	0/1 = 0	14/76 = 18.5%
Group III	2/15 = 13.3%	0/2 = 0	0/2 = 0	8/32 = 25.0%			10/51 = 19.6%
Total	22/89 = 24.7%	6/31 = 19.4%	8/32 = 25.0%	8/32 = 25.0%	0/6 = 0	2/10 = 20.0%	46/200 = 23.0%
	Grand mal predominating 28/120 = 23.3%				Petit mal predominating 2/16 = 12.5%		

Group I. Children with I.Q. over 80 and no evidence of neurologic lesion

Group II. Children with I.Q. less than 80 and no other evidence of neurologic lesion

Group III. Children with definite neurologic lesions

*The upper numeral in each instance indicates the number of remissions; the lower numeral, the total number of cases.

the liability to remissions between those patients having daily to weekly seizures and those having weekly to monthly seizures. Likewise there was no difference between those having monthly to quarterly attacks and those having quarterly to yearly attacks. However, there was a marked difference in the liability to remission when a comparison was made between those patients having attacks more frequently than monthly and those having attacks less frequently than monthly. This difference is shown in Table VI.

TABLE VI

RELATION OF REMISSIONS TO THE TOTAL NUMBER OF SEIZURES

FREQUENCY OF ATTACKS	MONTHLY OR MORE FREQUENTLY	LESS FREQUENTLY THAN MONTHLY	INTERMITTENT FREQUENCY
Group I	$\frac{9^*}{40} = 22.5\%$	$\frac{11}{27} = 40.8\%$	$\frac{2}{7}$
Group II	$\frac{6}{46} = 13.0\%$	$\frac{7}{16} = 43.8\%$	$\frac{1}{11}$
Group III	$\frac{3}{28} = 10.7\%$	$\frac{7}{18} = 38.8\%$	$\frac{0}{4}$
Total	$\frac{18}{114} = 15.8\%$	$\frac{25}{61} = 41.0\%$	$\frac{3}{22}$

*The upper numeral indicates remissions; the lower numeral, total number of cases.

Table VI shows that among 114 children, some of whom had attacks daily and others as infrequently as once a month, remissions occurred in about 16 per cent, whereas among 61 children having attacks less frequently than once a month, remissions were encountered in 41 per cent.

RELATION OF REMISSIONS TO THE TOTAL NUMBER OF SEIZURES

There are not complete records of the total number of attacks which occurred in all the cases of epilepsy studied. However, Table VII classifies all the patients with remissions according to the total number of attacks which had occurred.

TABLE VII

NUMBER OF ATTACKS WHICH OCCURRED IN PATIENTS HAVING REMISSIONS

NUMBER OF ATTACKS	NUMBER OF PATIENTS WITH REMISSIONS	
Less than 10 attacks	15	21 Mild cases
10-20 attacks	6	
20-50 attacks	6	6 Moderate cases
Hundreds of attacks	8	19 Severe cases
Innumerable attacks	11	
Total		46

It is seen that nearly half (21) of all the remissions were encountered in patients who had suffered very few attacks. However, 19 of the patients now free from seizures had had very severe forms of the disease.

RELATION OF REMISSIONS TO THE AGE AT ONSET

Table VIII records the age of the onset of epilepsy in all the 46 patients now free from attacks. It is seen that remissions were encountered irrespective of the age at which the disease began.

TABLE VIII

NUMBER OF PATIENTS WITH REMISSIONS—AGE AT ONSET OF EPILEPSY

AGE IN YR. AT ONSET	½	½-1	1	2	3	4	5	6	7	8	9	10	11	12	13	TOTAL
Number of remissions	6	2	4	5	6	2	3	3	2	2	1	7	0	0	3	46

AGE OF PATIENT AT TIME OF REMISSION

The age of the patients at the time of the last attack is recorded in Table IX.

TABLE IX

AGE IN YR. AT LAST ATTACK	>2	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	TOTAL
Number of remissions	0	1	0	6	3	4	2	3	3	5	5	4	5	0	3	2	46

It is seen that only one remission out of the 46 occurred in a patient less than four years of age. After the age of four, remissions were encountered in children of all ages.

DURATION OF EPILEPSY BEFORE REMISSIONS OCCURRED

Table X shows the duration of the disease prior to the occurrence of remissions.

TABLE X

DURATION PRIOR TO REMISSION	<1 YR.	1 YR.	2	3	4	5	6	7	8	9	10	11	12	TOTAL
Number of remissions	3	1	11	12	3	2	3	6	1	0	1	3	0	46

Most of the remissions were encountered in patients who had had attacks for periods of two to four years. Thirty of these cases were of less than five years' duration. Remissions were encountered in only 5 instances when the disease had lasted eight years or longer.

RELATION OF TREATMENT TO THE OCCURRENCE OF REMISSIONS

Remissions Occurring Without Medication.—Of the 9 patients whose attacks stopped while they were receiving no treatment, 5 had comparatively mild types of epilepsy with a total of less than 20 seizures. The other 4 patients had very severe forms with innumerable attacks occurring over periods of many years. Cases 1 and 2 are examples of spontaneous recoveries occurring in the mild and in the severe type, respectively.

CASE 1.—Mild epilepsy, stopping without medication. G. K. (H.L.H. No. 7849), male, white. Birth, development, and mentality were normal. Onset was in 1925, at ten years of age. Between August, 1925, and February, 1928, he had twelve

generalized convulsions without apparent cause. Two of these occurred in 1925, 6 in 1926, one in June, 1927, 2 in January, 1928. Two more attacks occurred in September, 1928, when he was 13 years old, but no attacks have occurred since. He never received any medication except for a few doses of phenobarbital immediately after each attack.

CASE 2.—Severe epilepsy stopping without medication. J. T. (H.L.H. No. 74283), male, with I.Q. of 67. Onset was in 1927, at age of seven and one-half years. Attacks were of the minor motor type. He would suddenly make automatic movements of his hand in front of his face. The attacks occurred every day, often every five or ten minutes. At the age of nine and one-half years, he began having seizures in which he would fall unconscious and hurt himself. There were no clonic movements. The attacks were followed by sleep. Six of those more severe seizures and numerous of the less severe variety occurred in the next two and one-half years. He was brought to the clinic in January, 1932, and 3 gr. of phenobarbital daily were prescribed. During the next month, no more severe attacks occurred, but the minor motor attacks continued at the rate of three to six per hour. In February, 1932, 3 gr. of phenobarbital and 30 grains of potassium borotartrate were prescribed. He never returned to the dispensary again, and, when his medicine was used up after a few weeks, no further drugs were taken. Frequent minor attacks continued until July, 1934, when they ceased spontaneously at the age of fifteen years.

Remissions Occurring With Medication in Patients Having Only a Few Attacks.—In reviewing the 37 cases that were under treatment at the time the attacks ceased, it was found that 14 patients had epilepsy of a very mild type. These children had had previously only four to ten attacks, usually spaced at long intervals. It was felt that when the attacks had previously been so infrequent, one was not justified in crediting the treatment with the cure, especially since in a number of instances all medication was discontinued within a few weeks after the last attack. Cases 3 and 4 are illustrative of this group.

CASE 3.—Patient with only five convulsions, which stopped while she was receiving phenobarbital medication. Medication discontinued shortly afterward. A. C. (H.L.H. No. 81859), colored, female, with approximately normal mentality. First attack occurred at 18 months, September, 1930. She had a total of 5 generalized convulsions: (1) September, 1930, (2) March, 1932, (3) June, 1932, (4) January 1933, (5) March, 1933. All attacks were of unknown origin, not accompanied by fever or gastrointestinal disturbance. At the age of four years she was brought to the clinic, and a daily dose of 1.5 gr. of phenobarbital was prescribed. A sixth attack occurred several weeks later, in April, 1933. No attacks have occurred since. All medication was discontinued almost immediately after the last seizure.

CASE 4.—Patient with only 10 convulsions, which stopped while he was receiving a small dose of phenobarbital. Medication was continued for four years after last attack. H. B. (H.L.H. No. 68691), white, male, with normal mentality. The first generalized convulsion occurred in July, 1927, when the patient was ten months old. It was possibly accompanied by fever. Following this, he had a generalized convulsion, without fever or other obvious cause, recurring every six months during the next three years. In the last ten days of September, 1930, four convulsions occurred, bringing the total to ten. Phenobarbital was begun with a dose of 0.75 gr. daily in September, 1930, when the patient was four years old. In October,

1930, the dose was reduced to 0.5 gr. No attacks occurred after the beginning of medication with the exception of a questionable abortive seizure in September, 1931. The phenobarbital was continued for three and a half years. In June, 1934, it was reduced to 0.25 gr. and was discontinued in November, 1934.

It is obvious that, when attacks have been as few as in Cases 3 and 4, one cannot be certain but that they may have ceased spontaneously. The incidence of remissions is very high in the group of epileptics without mental or neurologic defect who have had only a few generalized convulsions, usually spaced at long intervals. In a group of 18 cases belonging to this category that we have followed, 11 patients, or about 60 per cent, have now been free from attacks for long periods. Five of the 11 patients were receiving no treatment at the time the attacks ceased, and 6 were receiving sedatives. In these cases the convulsions occurred while the children were in good health, and *they were not associated with fever, infection, or gastrointestinal disorders.* They are, therefore, recurring convulsions of unknown origin and fulfill the commonly accepted criteria for the diagnosis of "essential epilepsy." It is certain that such cases occur much more frequently than our figures indicate. It is a common experience for the practicing physician to see children who have unexplained convulsions which recur several times a year for a number of years and then cease spontaneously. Such cases are frequently seen in the general pediatric dispensary. One hesitates to brand the children with the diagnosis of epilepsy unless the attacks recur frequently and persist. These cases are usually kept under observation, often without treatment. If the attacks cease—even after a dozen or more have occurred—they are usually diagnosed as "convulsions of unknown origin." In the diagnostic files of the Harriet Lane Home, there are 300 to 400 cases which have been so diagnosed. Many of the patients had undoubtedly "febrile convulsions," but many others might be diagnosed legitimately "epilepsy." If a child who has had comparatively few attacks, or whose attacks have continued for only a few months, is placed upon some special therapy, there is a probability of attributing the favorable outcome to the treatment employed, rather than to a spontaneous recovery.

Remissions Occurring With Medication in Patients Having Severe Forms of Epilepsy.—There were 23 patients having severe types of epilepsy with numerous attacks who ceased having seizures at a time when they were receiving sedative drugs. Six of these patients are still taking drugs; the other 17 have remained free after discontinuing all medication.

In certain cases there seemed to be a close correlation between the administration of sedatives and the control of attacks. Sometimes the attacks stopped abruptly when medication was begun, as in Case 5; sometimes there was a decided reduction in the frequency of the attacks

although they continued to occur for many months before ceasing entirely, as in Case 6. In other instances, grand mal seizures stopped after the administration of sedative drugs, but petit mal seizures continued for a long period before stopping eventually, as in Case 7.

CASE 5.—Patient with frequent localized convulsions over a long period, whose attacks stopped abruptly on the administration of potassium bromide. T. C. (H.L.H. No. 50765), white, male, with I.Q. of 40. There had been a sudden onset in September, 1925, at the age of fourteen months, with prolonged generalized convulsions followed by a left-sided paralysis which cleared up in about two months. A second attack occurred in December, 1925. There were two more in the next eighteen months. In October, 1927, he began having left-sided convulsions occurring in large numbers over a period of three or four days, followed by one- to two-week intervals of freedom. The condition continued unchanged until March, 1931, when at the age of seven and one-half years he was brought to the clinic. A daily dose of 30 gr. of potassium bromide caused the attacks to diminish. A month later (April, 1931) an increase in the dose to 37.5 gr. caused the attacks to stop immediately. None has occurred since. The same does of bromide was continued for ten months. It was decreased gradually and finally discontinued in July, 1933.

CASE 6.—Patient with frequent minor motor attacks, whose attacks were diminished by sedatives but did not stop entirely for one year. M. P. (H.L.H. No. 53065), white, female, mentally defective. Onset was in 1926, at the age of four years. The attacks were of the minor motor type and consisted of a sudden throwing out of the arms. They occurred from ten to fifty times a day. After one year she was brought to the clinic in April, 1927, at the age of five and one-half years. The administration of 2 gr. of phenobarbital caused temporary improvement but soon the attacks became more frequent than ever, occurring almost continuously, and a phenobarbital rash appeared. In May, 1927, the treatment was changed to sodium bromide, 30 gr. daily. The attacks then decreased to one to four daily. Bromide therapy was continued, although the dose was varied slightly and phenobarbital was given another short trial. Under bromides the attacks continued to occur one to three times a day until May, 1928, when they stopped entirely. All medication was discontinued a few weeks later, without any recurrence of seizures.

CASE 7.—Patient started with generalized convulsions. Under medication attacks changed to the petit mal type and then ceased. A. D. (H.L.H. No. 74304), white, female, with an I.Q. of 77. She began to have generalized convulsions in 1926, at two years of age. They occurred two to three times a year until October, 1931, when she was brought to the clinic, at the age of seven and one-half years. A daily dose of 20 gr. of potassium bromide and 0.5 gr. of phenobarbital was prescribed. The parents were not very cooperative, and medication was at times interrupted. After beginning sedatives no more convulsions occurred but a varying number of petit mal attacks were observed until October, 1933, when they stopped entirely. Medication was continued until August, 1935. It has subsequently been discontinued without ill effect.

In cases of the types cited above, the improvement and the cessation of attacks seemed to be directly related to the administration of sedatives. In other instances, however, the relationship of remissions to therapy was more obscure. This is especially true in the case of certain patients who showed no improvement under medication for long periods of time and then, without appreciable change in the treatment,

became improved and free from attacks. An example of this response is Case 8. In a number of instances the remission dated from an intercurrent acute infection.

CASE 8.—Patient with severe epilepsy, who for two years showed no improvement under large doses of sedatives. Without change in treatment, the attacks suddenly decreased in number and then stopped. K. K. (H.L.H. No. 29714), white, female, normal mentality. In 1920 at the age of three years she began having minor motor attacks occurring daily, frequently as many as fifteen. Four generalized convulsions also occurred in the next eighteen months. Phenobarbital was begun in 1921, and a period of starvation was tried. Although there were periods of slight improvement, there was no striking benefit. In June, 1922, a prolonged period of status epilepticus necessitated the daily administration of 6 gr. of phenobarbital, 5 gr. of chloral hydrate, and 15 gr. of potassium bromide. In spite of these heroic doses, during the next nine months the attacks remained very frequent, amounting at times to status. In March, 1923, at the age of six years, the attacks suddenly decreased in frequency; the chloral and bromide were discontinued, and phenobarbital was reduced to 4.5 gr. Only one attack occurred in March, 1923. After this the child had one attack monthly and during the spring and summer of 1923 the phenobarbital was gradually decreased to 0.5 gr. In December, 1923, the patient developed pertussis, and her attacks ceased entirely. Phenobarbital was discontinued at the same time. She has remained well since—a period of twelve years.

In two other instances we have observed the termination of epileptic seizures to occur simultaneously with the onset of an acute infection; in one instance measles, in the other pneumonia.

DISCUSSION

Among the 200 epileptic children studied, remissions of one year or longer were encountered in 46 or 23 per cent, and remissions of two years or longer in 19 per cent. These figures correspond very closely to those of other workers. Even before bromides were introduced in 1857, "cures" were reported by Hufeland[2] in 5 per cent of cases, by Russell Reynolds[2] in 10 per cent, and by Trousseau[2] in 13 per cent. In 1903 Turner studied 212 patients of all ages with "idiopathic" epilepsy, who had been constantly under bromide treatment. He found that remissions of two years or longer occurred in 33 per cent of the patients. The prognosis for remissions was poorest when the disease had begun under ten years of age. In a group of 111 patients whose disease began in the first decade and who, therefore, correspond to our patients, remissions of two years or more occurred in 19.8 per cent. Lennox[4] in 1930 investigated over 1,000 case histories of noninstitutionalized epilepties of all ages and found that 23 per cent had had remissions lasting more than one year and 6 per cent remissions for more than five years. Clemmesen and Moltke[5] in 1934 examined 100 children who had been diagnosed as having epilepsy five to fifteen years previously and found that 25 had been free from attacks for two years or more. On the other hand, in dealing with mentally defective epilepties in the Craig Colony, Spratling[6] found only a 5 per cent expectancy of "cure."

In our opinion the principal factors which influence the prognosis for remissions are the number and frequency of attacks. We found the incidence of remissions to be 41 per cent in patients whose attacks occurred less frequently than monthly as compared with 16 per cent in patients having attacks monthly or more often. When a patient has had only a few attacks, less than 10 or 20, spaced at long intervals, the prognosis for a long remission, and possibly for permanent "cure," is especially favorable. Among 18 patients of this type, 11 (or 60 per cent) have now been free from attacks for long periods. Although we have no accurate figures to prove it, we believe that many patients are encountered in private practice and the general dispensaries who have occasional unexplained convulsions over a number of years and eventually make a permanent recovery. Turner[3] found the same variation in the outlook according to the frequency of the seizures. Among those patients whose attacks occurred weekly or more frequently the incidence of two-year remissions was 12.5 per cent, as contrasted with an incidence of 37 per cent when attacks occurred quarterly, and 42 per cent when attacks occurred once or twice a year.

We found that remissions occurred in approximately 30 per cent of the children with approximately normal intelligence and without neurologic lesions, whereas they were encountered in only about 20 per cent of the cases associated with mental defects or with neurologic lesions. It is possible that the higher proportion of mild cases (i.e., patients with few and infrequent seizures) in the former group[1] may account for the more favorable prognosis. Lennox[4] states that the outlook is more favorable when evidence of a neurologic lesion is lacking and when the intelligence is normal.

Remissions occurred twice as frequently (23 to 25 per cent) in patients having generalized convulsions, localized convulsions, or minor motor seizures as in those whose attacks were predominantly of the true petit mal type (12.5 per cent). Turner also found that arrests occurred most frequently in cases of the major type, next in cases having combined major and minor fits, and least in minor epilepsy occurring alone.

Thirty of the 46 remissions which we encountered were in patients whose disease was of less than five years' duration. Turner found an incidence of 27 per cent remissions in cases of less than five years' duration, as compared with 11.5 per cent in cases which had lasted five to ten years.

The age of the patient at the onset of epilepsy seemed to have no influence on the liability to remission in the children studied. Only one remission out of the 46 occurred in a patient less than four years of age. After the age of four, remissions were encountered in children of all ages.

It is a very difficult matter to evaluate the influence of therapy in causing the cessation of attacks. Nine of the children were receiving

no medication at the time their seizures stopped. Although 5 of these patients had mild types of epilepsy with few and infrequent convulsions, the other 4 had very severe forms with innumerable attacks occurring over periods of many years. There were no hygienic or psychic adjustments evident to account for their improvement. Of the 37 patients who were receiving medication at the time of remission, 14 had mild forms of epilepsy, of the type which we believe is liable to spontaneous recovery. However, the remaining 23 patients whose attacks stopped under treatment were suffering from severe forms of epilepsy of long duration. In some cases the beneficial influence of sedative drugs was evidenced by the immediate cessation of attacks upon the beginning of treatment or by a gradual improvement followed finally by freedom from seizures. In other cases, however, sedative therapy seemed to exert no influence for a long period of time and then, without any change in treatment or any obvious cause, there were sudden improvement and cessation of attacks. *We do not wish to imply that sedative drugs do not exert a favorable influence in most cases of epilepsy, decreasing the frequency and severity of seizures and, in some instances, stopping the attacks entirely. We wish merely to point out that spontaneous remissions may occur even in the most severe cases and that it is an exceedingly difficult matter to evaluate any therapeutic "cure."*

The prognosis for permanent recovery we are unable to discuss on the basis of our own experience. Patients would have to be followed for a lifetime to discover how frequently relapses occur after long periods of remission. Adult epileptics frequently give a history of having had long remissions during the period of adolescence with a recurrence of the disease in the late teens or the twenties. Turner found that, after patients had remained free from attacks for eight or nine years, relapses occurred very rarely. He states, "It is unsafe to regard as cured any case of epilepsy in which the seizures have been in abeyance for a period less than nine years." Of 147 cases (of all ages) which he followed, 15 (or 10.2 per cent) remained free from seizures for over nine years and might be considered "probably cured."

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EPILEPSY IN CHILDHOOD

III. Results With the Ketogenic Diet

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THE results obtained in the treatment of epilepsy in childhood by the ketogenic diet have been reported by Peterman,[1] Helmholz,[2] Talbot,[3] Eley,[4] Pulford[5] and others and in adults by Barborka,[6] Doolittle,[7] Bastible,[8] and Notkin.[9] However, many of these papers present only meager clinical descriptions of the cases treated and fail to describe the response of the patient to treatment.

Although over 400 children have come under observation in the Epilepsy Clinic, either poverty or lack of intelligence or cooperation has prevented a satisfactory trial of the ketogenic diet in all except a small number of cases. The diet was attempted in forty cases,* but six patients failed to cooperate sufficiently well to permit any judgment of the results and have been discarded from the series. Two other patients who failed to respond to the diet have been ruled out because they had definite neurologic lesions. Two others were under observation for only a very short period, and their status is not known. The remaining thirty patients upon whom the present report is based are those who have been maintained in ketosis for a sufficient length of time to warrant a judgment of its effect on the course of the disease. In most instances the patients have cooperated excellently. Any failure in cooperation has been given recognition in the discussion of the results obtained.

In general the usual ketogenic regime employed by other workers has been followed and a diet with F : C + P ratio of 4 :1 has been given. In many cases the diet was preceded by a starvation period of three to seven days. Since every effort was being exerted to stop the patients' seizures, it was often found advisable to combine other therapeutic measures with the ketogenic diet. From the scientific point of view this was unfortunate because in some instances it was impossible to determine whether the improvement was due to the diet or to some other measure. However, it is true that most of the patients had failed previously to respond to sedatives and other measures of treatment. The restriction of fluid intake, the production of acidosis by means of ammonium chloride, the administration of low salt diets and of theobromine sodium salicylate have all been tried in certain cases. Sedative

From the Harriet Lane Home of the Johns Hopkins Hospital and the Department of Pediatrics of the Johns Hopkins University School of Medicine. Aided by the support of the Epilepsy Medical Research Fund and The John Howland Memorial Fund.

*These patients were treated under the supervision of Dr. Edward M. Bridge, Dr. Laslo Kajdi, or the author. In many instances detailed chemical and metabolic studies were made by Dr. Bridge or Dr. Kajdi.

drugs, such as phenobarbital and bromides, have been added to the treatment of most patients not otherwise benefited. It must be emphasized that the patients reported as not benefited, or improved only temporarily, frequently have been treated more intensively than any others. In some instances these children have been brought into the hospital repeatedly for exhaustive studies; they often have been given repeated starvation periods and every method of treatment has been tried before they were considered definitely unchanged.

RESULTS OF TREATMENT WITH KETOGENIC DIET

The results obtained by the treatment with the ketogenic diet are shown in Table I.

TABLE I

Complete freedom from attacks, now on normal diet	8 patients
Temporary freedom from attacks, relapse while on ketogenic diet	4 patients
Possible temporary improvement	3 patients
No benefit	15 patients

Each of these groups will be discussed in more detail in later sections. It is of interest here to determine whether the results were influenced by the selection of a particularly favorable group of patients, as we[10] have shown that in a group of children treated by other means than diet, the prognosis for remissions may vary according to the type of epilepsy, the character of the attack, and the severity of the disease.

TYPE OF EPILEPSY AND SEVERITY OF CASES TREATED

The 30 patients reported presented *no evidence of organic cerebral lesions*, either in their history, neurologic examination or x-ray of the skull. Encephalograms were not made in most instances. All of these children except three had intelligence quotients above 80. These three had I. Q.'s of 78, 78, and 76, respectively. Most of the patients were of rather high intelligence as shown in Table II.

TABLE II

INTELLIGENCE QUOTIENT	NUMBER OF PATIENTS TREATED	FREE FROM ATTACKS
100 or over	6	3
90-99	14	4
80-89	7	1
76-79	3	0
	30	8

The group may therefore be compared with the patients with I. Q.'s above 80 and without neurologic lesions, as reported in our previous papers.[10] It is possible that the prognosis for remission is slightly better in this group than in that in which a mental or neurologic defect occurs.

The frequency of seizures in the patients treated is shown in Table III.

TABLE III

FREQUENCY OF ATTACKS	NUMBER OF PATIENTS TREATED	FREE FROM ATTACKS
Daily to weekly	26	6
Weekly to monthly	1	0
Monthly to quarterly	1	1
Remitting type	2	1
	30	8

It is apparent from these figures that the children selected for treatment with the ketogenic diet in nearly all instances were subject to very frequent seizures. Six of the eight patients who became free from attacks had a severe form of epilepsy. In one instance the attacks were infrequent and few, and in one instance the patient had been subject to previous remissions. In a previous paper[10] dealing with children not treated by the ketogenic diet, it has been shown that remissions are encountered much less frequently in the severe forms of epilepsy than in the milder types. Among patients having attacks more frequently than monthly, the incidence of remissions was 16 per cent as compared to 40 per cent when the attacks occurred less frequently.

RELATION OF RESULT TO THE CHARACTER OF ATTACK

In Table IV we have recorded the result obtained in the various kinds of attacks treated.

TABLE IV

TYPE OF ATTACK	ATTACKS STOPPED ENTIRELY	PERIOD OF FREEDOM THEN RELAPSE	POSSIBLY TEMPORARY IMPROVEMENT	NO BENEFIT	TOTAL	FREE FROM ATTACKS
Grand mal	2	0	1	1	11	4
Grand mal with petit mal or minor motor attacks	2	2	0	3		
Minor motor attacks	1	0	1	4	6	1
Petit mal with occasional grand mal	2	1	1	3	13	3
Only petit mal	1	1	0	4		
Total	8	4	3	15	30	8

These groups are too small to be of statistical value. However, it is seen that a considerable proportion of the patients treated had attacks of the petit mal type, which has been found to be less subject to remissions than other types.[10] Of thirteen patients whose attacks were predominantly petit mal, three became free from attacks.

PATIENTS FREE FROM ATTACKS

In Table V are summarized the pertinent facts in regard to the patients who responded to ketogenic therapy. In order to give a clearer picture of the nature of the response, it is necessary to discuss these cases in more detail.

CASE 1.—S. W., female, a private patient, aged thirteen years, at the beginning of treatment. A history of chewing paint, and a sudden onset with a series of left-sided convulsions at the age of two years, and some disturbances in the gait and speech suggested that she may have had a lead encephalopathy at that time. The convulsions continued, but at the age of nine years the character changed. From then on the attacks consisted of tonic convulsions with loss of consciousness but without localization. For eleven years she had been treated with phenobarbital, bromides, and belladonna in various combinations without any effect. Menstruation, which had begun at eleven and one-half years, had caused no change in the disease. When she came under observation at thirteen years of age, the neurologic examination was negative, there was only slight mental retardation, and there were no evidences of lead poisoning. At this time she was having four or five seizures daily for a number of days followed by free intervals of not over three or four days. Treatment was begun March, 1929, with a starvation period of two days followed by a ketogenic diet, beginning with a 2:1 ratio and increasing within a week to a 4:1 ratio. The patient had been receiving phenobarbital 1 gr. each night, and this was continued. Although the administration of the ketogenic diet caused an immediate diminution in the number of seizures, the attacks continued for four months, ceasing only after the dose of phenobarbital had been increased to 3 gr. daily. After freedom from attacks for four months, phenobarbital was withdrawn, and after a further period of six and one-half months, in January, 1930, a sudden shift from the 4:1 ketogenic diet to a dehydration regime with an otherwise unrestricted diet caused no relapse. A study of the fluid balance at the time of this transition indicated that the ketogenic diet had already reduced the fluid stores of the body. A rigid restriction of fluid intake to 300 to 400 c.c. was maintained for two years (until January, 1932). There have been no attacks since August, 1929 (a period of six and one-half years), although during the past year two or three episodes have occurred which were probably hysterical rather than epileptic. Her cooperation with treatment was excellent throughout.

CASE 2.—N. L. (H.L.H. No. 59406), male, aged five one-half years at time of treatment. "Idiopathic" epilepsy. I. Q. was 110. Onset was at four years. Eleven generalized convulsions in the course of the first year. The convulsions then stopped spontaneously, and petit mal seizures occurred instead, increasing in frequency up to 10 or 12 daily. After the petit mal attacks had continued for six months unaffected by 1.5 gr. of phenobarbital daily, in March, 1929, the ketogenic diet was begun gradually without preliminary starvation. In the course of six weeks the ratio was increased from 1:1 to 4:1. The administration of 1.5 gr. of phenobarbital was continued. There was no improvement for two months. Then, following several vomiting episodes which caused some dehydration, the attacks stopped entirely in May, 1929. Between June and October, 1929, the phenobarbital was gradually discontinued. A 3.5:1 diet was maintained until March, 1930, nine months after the attacks had stopped. The diet was then decreased by degrees to a 1:1 ratio in October, 1930. This ratio was maintained until November, 1932. Since then the boy has taken an unrestricted diet. There have been no attacks since May, 1929, a period of six and three-fourths years. Cooperation with treatment was excellent throughout.

CASE 3.—T. S. (H.L.H. No. 78510), male, aged nine and one-half years at time of treatment. "Idiopathic" epilepsy. I. Q. was 97. The patient had a convulsion at four years and then no further seizures until he was seven and one-half years, in January, 1930. Petit mal seizures then occurred, increasing up to ten daily. Between July, 1932, and January, 1933, phenobarbital and prominal and potassium borotartrate were tried without effect. In February, 1933, following a starvation period of four days, a 4:1 ketogenic diet was begun. From then until September,

1933 (a period of seven months), only occasional attacks were noted at rare intervals, and these were supposedly associated with breaks in the diet. The 4:1 diet was maintained until October, 1934, a period of eighteen months. Then an attack of acute rheumatic fever caused the diet to be discontinued. He has subsequently taken a normally balanced diet but has had some severe exacerbations of acute rheumatic fever with pericarditis and myocardial insufficiency. No attacks have occurred since September, 1933, a period of two and one-half years. The patient's cooperation on the diet was fair although there were occasional breaks during the first year of treatment.

CASE 4.—C. W. (H.L.H. No. 85881), male, aged seven years at time of treatment. "Idiopathic" epilepsy. I. Q. was 99. Onset was in September, 1933, at age of six and one-half years, with typical petit mal attacks occurring three or four times a day. There were never any convulsions. Daily doses of 30 gr. of potassium bromide and 30 gr. of potassium borotartrate were begun in January, 1934, but in March, 1934, attacks became so numerous that the patient was in a constant daze. In May, 1934, he was having two to seven attacks daily. Lumbar puncture and an air injection were performed May 9, 1934, and a tonsillectomy May 17. In June, 1934, after a starvation period of four days, a 4:1 ketogenic diet was begun. No drugs were given. No more attacks occurred. The 4:1 diet was maintained until March, 1935, and since then decreased to 3:1. In November, 1935, the diet was discontinued entirely. No attacks have occurred since the diet was first begun in June, 1934, a period of twenty-one months. However, he has taken an unrestricted diet for only the past six months, a period too short to be sure that a relapse may not occur.* Cooperation was excellent throughout treatment, and ketosis was well maintained.

CASE 5.—N. A., male, a private patient, aged seven and one-half years at time of treatment. "Idiopathic" epilepsy with minor motor manifestations and also generalized convulsions. I. Q. was over 100. Ketogenic diet was begun in October, 1928, after the attacks had been occurring for only one month. No drugs were administered before treatment or during the first two years of diet. Attacks were as frequent as six a week. The diet was begun gradually, increasing by degrees to a 4:1 ratio. Definite improvement was not shown for four months. There was then marked improvement, although during the next eighteen months the patient continued to have one to three seizures monthly. These attacks were apparently associated with breaks in the diet. In September, 1930, the administration of 1 gr. of phenobarbital at bedtime was begun, and the attacks stopped entirely, in spite of the fact that at this time the patient began to break the diet more and more, and ketosis was no longer well maintained. During the next six months the attempt to restrict him to a 3:1 diet was unsuccessful. Finally dietary restriction was entirely discontinued in June, 1931. Phenobarbital was withdrawn in September, 1931. The patient has had no attacks since September, 1930, a period of five and one-half years. The increasing failure in cooperation and the administration of a small dose of phenobarbital at the time the attacks ceased make it difficult to evaluate the effect of therapy.

CASE 6.—C. W. (H.L.H. No. 61086), male, aged four years at time of treatment. Possibly slight mental retardation. "Idiopathic" epilepsy with both convulsions and petit mal attacks. Onset was at the age of eighteen months. At times the seizures were very infrequent, at other times there was status epilepticus. The seizures appeared to be influenced favorably by chloretone, but not by phenobarbital. After a duration of two years, in February, 1929, the patient was put on a ketogenic diet without preliminary starvation. The fat ratio was increased gradually to 4:1. Chloretone was also given. In spite of the fact that the diet was rigidly

*Patient was still free from attacks in May, 1936.

followed, the patient continued, until June, 1929, to have one to ten convulsions daily and on some days hundreds of minor attacks. The attacks then ceased abruptly without any change in the regime. There was no recurrence in spite of the fact that after this period the boy began to break his diet constantly and had no diacetic acid in the urine. The mother attempted with doubtful success to restrict him to 4:1 diet until March, 1930. The fat ratio was then decreased by degrees and in April, 1931, he resumed a normal diet. An attempt was made to restrict his fluids to 14 to 16 ounces daily, but it is doubtful if there was close cooperation. He continued to receive chloretone and bromides until June, 1931. Since then he has had no treatment. He has now been free from attacks since June, 1929, a period of six and three-fourths years. The simultaneous administration of drugs and the failure to maintain a rigid ketosis soon after the attacks ceased make the interpretation of the result difficult.

CASE 7.—D. S. (H.L.H. No. 71343), female, aged eight and one-half years at time of treatment. "Idiopathic" epilepsy. Normal mentality. Onset was on Feb. 12, 1931. Generalized convulsions were repeated a number of times each day, but there were sometimes free intervals of three or four days. Phenobarbital seemed to lessen the severity, but not the frequency, of the attacks. After six weeks the child was given a preliminary starvation period of five days, and on April 1, 1931, she was restricted to a 4:1 ketogenic diet. In addition to the diet, she was treated with potassium bromide. There was no definite effect on the course of the disease until the bromide was increased to 30 gr. daily in August, 1931. There were then no attacks until September 4, and following this no more until March 15, 1932. It had been increasingly difficult to keep her on the diet, and the fat ratio had been decreased to 2:8:1 in October. In January, 1932, the bromide was reduced to 20 gr. daily. There was a mild convulsion March 15, 1932, and another Aug. 25, 1932. In the fall of 1932 occasional petit mal attacks were noted. In November, 1932, the bromide was again increased to 30 gr. a day, and the administration of potassium borotartrate 30 gr. daily was begun. The attacks stopped at that time. A borderline ketogenic diet of 2.5:1 ratio was continued until May, 1932. The ratio was then decreased to 1.5:1, and the diet was discontinued in September, 1933. Bromide and borotartrate were continued for some months afterward. No attacks have occurred since November, 1932, a period of three and one-half years. The apparent relation of the bromide to the control of the attacks makes it difficult to evaluate the influence of the ketogenic diet.

CASE 8.—P. M. (H.L.H. No. 65108), female, aged three years and ten months at time of treatment. I. Q. was 104. The child had only four series of generalized convulsions over a period of ten weeks on the following dates: Nov. 23, 1929, Dec. 3, 1929, Jan. 5, 1930, and Feb. 1, 1930. The first three were single generalized convulsions without apparent cause. On Feb. 1, 1930, she had severe "cramps in the abdomen," vomited, seemed very jumpy, and occasionally twitched. She seemed sick all day. Throughout the night and the following day convulsions occurred at four- or five-hour intervals. The patient seemed well for two days, but on February 5 from 5 to 7 A.M. she had almost continuous convulsions. On March 4 and March 5, 1930, the patient was given 3 ounces of 40 per cent cream and two ounces of orange juice three times daily, and on March 6 she was put on a diet of 3.5:1 ratio. Fairly good ketosis resulted. She was also given 1.5 gr. of phenobarbital daily. No more attacks occurred. In August, 1930, the fat ratio was decreased to 3:1 and the phenobarbital to 0.75 gr. In November, 1930, the phenobarbital was discontinued. Between January, 1931, and November, 1932, the fat ratio was gradually reduced, the diet being entirely discontinued in November, 1932. There have been no attacks since February, 1930, a period of six years. The fact that this patient had had only four series of convulsions prior to treatment makes it difficult

to evaluate the effect of the ketogenic diet. It is not uncommon to encounter children who have a few convulsions without obvious cause, which continue over a period of some months and then cease spontaneously, never to recur.

COMMENT

The results in these eight cases have been very satisfactory (see Table V). Four patients have been free from attacks for over six years, one for over five years, and one for three years, one for two and one-half years, and one for one and one-half years. All the patients have been able to resume an unrestricted diet without relapse. In all except Case 4 a sufficient period without restriction (from one and one-half to six years) has elapsed now to justify the belief that further treatment is not necessary. In only Cases 4 and 8 did the attacks stop immediately after the diet was begun. In the other six cases, intervals varying from three months to twenty-three months elapsed before the seizures ceased entirely. The F: C + P ratio of 4:1 was maintained for a period varying from one to two years in six cases, in one case for six months, and in one case for three months. In most instances the ketogenic ratio was decreased by degrees so that a total period of ten to thirty-two months elapsed before an unrestricted diet was resumed.

In reviewing these eight cases, it is difficult to determine how much credit for the successful result should be attributed to the ketogenic diet. Seven of the patients had severe forms of epilepsy; the eighth patient, however, had had only a few episodes scattered over three months and accordingly was of a type more prone to cease spontaneously. Before the ketogenic diet was begun, the disease had lasted for one month in one case, three months in one case, six to eight months in two cases, one to three years in four cases, and eleven years in one case. Prior to the dietary treatment, sedative drugs had been tried without striking effect in all except one instance (Case 5). Simultaneously with the ketogenic diet, sedative drugs were administered in all but Cases 3 and 4. In one case (Case 7) in which bromides were given, the favorable result seemed to be due more probably to the bromide than to the ketosis, as the attacks ceased only when the dose of bromide was increased to 30 gr. and recurred when it was later reduced to 20 gr. In two other cases (Cases 1 and 5) the addition of phenobarbital to the dietary therapy seemed closely associated with the cessation of attacks. The cooperation of the patients in adhering to the diet and maintaining a high degree of ketosis was perfect in only four instances (Cases 1, 2, 4, and 8). In the other four instances, there were occasional breaks in the diet, and at times the breaks seemed to be associated with a recurrence of the attacks, although one could not always be certain of the association. In two cases (Cases

TABLE V

PATIENTS FREE FROM ATTACKS

SERIES NO.	NAME	SEX	H.L.H. NO.	CHARACTER OF ATTACK	FREQUENCY	AGE AT ONSET (YR.)	AGE WHEN DIET WAS BEGUN (YR.)	DURATION BEFORE KETOGENIC TREATMENT	PREVIOUS TREATMENT RESULTS	PRELIMINARY STARVATION (DAYS)	ADDITIONAL TREATMENT AT TIME WHEN ATTACKS STOPPED	INTERVAL BEFORE ATTACKS STOPPED (MO.)	TIME ON 4:1 DIET (MO.)	TIME BEFORE NORMAL DIET (MO.)	TIME SINCE LAST ATTACK (YR.)	TIME SINCE NORMAL DIET RESUMED (YR.)	COOPERATION
1	S. W.	F.	Pvt. pt.	Minor motor	Daily-weekly	2	13	11 yr.	Ph. Br. No improvement	2	Ph. 3 gr.	4½	10	10	6½	6	Good
2	N. L.	M.	59406	Grand mal Petit mal	Total of 11 G.M. P.M. 10-12 daily	4	5½	17 mo.	Ph. G.M. stopped P.M. continued	0	Ph. 0.75 gr.	3	12	32	6½	3½	Good
3	T. S.	M.	78510	Petit mal Grand mal	2-7 daily One only	7½	10½	3 yr.	Ph. Pr. Btr. No improvement	4	0	8	18	19	2½	1½	Occasional break
4	C. W.	M.	85881	Petit mal	2-7 daily	6½	7	8 mo.	Br. and Btr. No improvement	4	0	0	18	18	1½	½	Good
5	N. A.	M.	Pvt. pt.	Minor and Grand mal	Daily-weekly	7	7	1 mo.	None	0	Ph. 1 gr.	23	24	31	5½	4½	Poor at time of cure
6	C. W.	M.	61086	Grand mal Petit mal	Intermittent	1½	4	2½ yr.	Ph. and Br. No improvement Chloretone Improved	0	Chloretone and Br.	4	13	30	6½	5	Poor
7	D. S.	F.	71343	Grand mal	Daily-weekly	8	8½	6 mo.	Ph. Improvement	5	Br. 30 gr.	19	6	29	3½	2¾	Poor
8	P. M.	F.	65108	Grand mal	Total of 5 in 4 mo.	3½	8¾	3 mo.	Ph.	0	Ph. 0.75 gr.	0	3	32	6	3½	Good

Ph=phenobarbital; Br=bromides; Btr=potassium borotartrate; Pr=prominal.

5 and 6) the final cessation of attacks came at the very time when the patients were becoming more and more lax in the maintenance of the regime.

To summarize our impression in looking back over these clinical histories, the diet seems to have been closely associated with the favorable result in four patients with severe forms of epilepsy (Cases 1, 2, 3, and 4). Two of these four patients received sedatives and two no drugs. In two other patients (Cases 5 and 6) the results are confused by the increasing laxity in the diet at the time of improvement and also by the simultaneous use of drugs. In the seventh case the result could be attributed as readily to bromide as to the diet. The eighth patient had had only a few epileptic episodes over a three-month period and was of a type especially prone to spontaneous remissions.

PATIENTS WHO HAD TEMPORARY PERIOD OF FREEDOM FOLLOWED BY RELAPSE

Table VI summarizes the important facts concerning the four patients who had fairly long remissions while receiving the ketogenic diet but afterward had relapses.

Their histories are abstracted in detail below.

CASE 9.—A. M. (H.L.H. No. 75355), female, aged twelve and one-half years at time of treatment. Idiopathic epilepsy. I. Q. was 100. Petit mal with three convulsions. Onset was in December, 1930, at the age of eleven years. Attacks increased in frequency up to 2 to 5 daily. From December, 1931, to June, 1932, treatment with phenobarbital, bromides, and potassium borotartrate caused no improvement. In June, 1932, after a preliminary starvation of four days, a 4:1 ketogenic diet was begun. No drugs were administered. Petit mal attacks stopped for two weeks, then one generalized convulsion occurred. Following this occasional petit mal attacks were observed until August, 1932. No attacks occurred from August, 1932, until October, 1933, a period of fourteen months. The diet was then reduced to a 3:1 ratio, and one or two petit mal attacks began to occur each month at about the time of the menstrual period. Between October, 1933, and October, 1935, attacks continued but never became more frequent. It was then decided to remove gradually the dietary restrictions. (According to the last report, June, 1936, the patient was receiving practically a normal diet, and no attacks had been observed for the preceding three months.)

CASE 10.—M. P. (H.L.H. No. 64040), female, aged nine and one-half years at time of treatment. Idiopathic epilepsy. I. Q. was 100. Petit mal attacks only. Onset was at eight years of age. Many attacks occurred every day. She had failed to respond to phenobarbital and bromides. After the illness lasted ten months, she was put on a 2:1 diet, increased to 4:1 at the end of three weeks. She received no drugs. The attacks gradually became less frequent and then ceased after three months. The child was then free from attacks for fifteen months. After the first six months of treatment, the fat ratio had been reduced gradually from 4:1 to 2:1. Although the patient had been very cooperative at first, at the end of this fifteen-month period she had begun to break the diet. The petit mal attacks now gradually returned. The child was put back on a 4:1 diet, but good cooperation could no longer be obtained, and ketosis was not constant. The ad-

TABLE VI

TEMPORARY FREEDOM FROM ATTACKS FOLLOWED BY RELAPSE

SERIES NO.	NAME	SEX	H.L.H. NO.	CHARACTER OF ATTACK	FREQUENCY	AGE AT ONSET (YR.)	AGE WHEN DIET WAS BEGUN (YR.)	DURATION BEFORE KETOGENIC TREATMENT	PREVIOUS TREATMENT RESULTS	PRELIMINARY STARVATION (DAYS)	ADDITIONAL TREATMENT AT TIME ATTACKS STOPPED	INTERVAL BEFORE ATTACKS STOPPED	TIME ON 4:1 DIET (MO.)	TIME BEFORE NORMAL DIET RESUMED (MO.)	DURATION OF FREEDOM (MO.)	STATUS OF TREATMENT AT TIME OF IMPROVEMENT	STATUS OF TREATMENT AT TIME OF RELAPSE
9	A. M.	F.	75355	Petit mal 3 grand mal	2-5 daily	11	12½	18 mo.	Ph. Br. Btr. No improvement	4	0	2 mo.	16	48	14	4:1 Good ketosis	3:1 Good ketosis
10	M. P.	F.	64040	Petit mal	2-20 daily	8½	9½	10 mo.	Ph. Br. No improvement	0	0	3 mo.	12	32	15	4:1 Good ketosis	2:1 Poor ketosis Breaking diet (†)
11	L. D.	F.	60090	Petit mal Previous grand mal and minor	4-6 daily	6	8½	2½ yr.	Ph. Freedom for 10 mo.	5	0	2 days	3	19	12	4:1 Good ketosis	2:1 Poor ketosis Breaking diet
12	S. B.	F.	Pvt. pt.	Minor motor	30 daily Intermittent type	8	8	2 mo.	Ph. No improvement	0	0	23 mo.	40	40	9	Cycle of improvement and relapse without close relation to degree of ketosis	

dition of phenobarbital and potassium borotartrate was ineffectual, and gradually the attacks returned to the same level of frequency as before treatment. Finally after thirty-two months the ketogenic diet was discontinued entirely.

CASE 11.—L. D. (H.L.H. No. 60090), female, aged eight and one-half years at time of treatment. Idiopathic epilepsy. I. Q. was 78. Convulsions, minor motor attacks and petit mal. Onset was at six years. For the first fifteen months there were frequent convulsions, followed by a period of ten months of freedom while receiving phenobarbital. The child then began to have four to six minor attacks daily. These continued for five months and were not controlled by phenobarbital. After a preliminary fast of five days, the patient was restricted to 4:1 ketogenic diet. The attacks stopped the second day, and no more occurred during the next twelve months. No drugs were administered during this period. During the first six months of freedom, the fat ratio was 4:1 to 3:1; during the next six months it was reduced gradually to 2:1. Near the end of the twelve-month period the patient began breaking her diet. The attacks then began to recur, and some petit mal attacks were occurring daily interspersed with occasional convulsions. The child continued a 2:1 diet for another six months but did not cooperate well and finally discontinued the diet. Subsequently phenobarbital, bromides, and borotartrate have had little effect.

CASE 12.—S. B., female, a private patient, aged eight years at time of treatment. Idiopathic epilepsy. Slight mental retardation. Onset was at eight years with minor motor attacks occurring as often as thirty daily. Phenobarbital was of no apparent benefit. After two months drug therapy was discontinued and a ketogenic diet was begun and was increased gradually to 4:1 ratio. The attacks decreased markedly in number, averaging one each night, for the first six months of dietary therapy. During the next eight months, the child was still better, having only one to four attacks each month. She then returned to school and began to break her diet. The attacks increased in frequency up to five each night. The child was put in a nursing home under strict supervision for several months, but in spite of this she showed no improvement for nine months. Then, without apparent reason, the attacks ceased entirely for a period of nine months. The attacks then recurred, one to three each night, and occasional attacks began to appear in the daytime. About this time the girl became more and more uncooperative, constantly stealing food and breaking her diet. Finally after a trial of forty months, the diet was discontinued and instead 0.75 gr. of phenobarbital was administered each night at bedtime. With the stopping of the ketogenic diet and the substitution of phenobarbital, the child again had a six-month period of freedom followed by another relapse.

COMMENT

Four children treated by the ketogenic diet had periods of freedom from attacks lasting for nine months to fifteen months. Subsequently relapses occurred, and eventually the diet was discontinued. Drugs were not administered to any of these patients at the same time as the diet. In only one (Case 9) did the patient's cooperation in the diet remain perfect. In the other three (Cases 10, 11, and 12) the relapse was associated with increasing laxity in the diet and failure in the maintenance of ketosis. In two (Cases 11 and 12) it is difficult to know whether the temporary remission was brought about by the diet because the attacks, either before or after ketogenic treatment, were very variable in frequency and at times there were periods of freedom from attacks.

TABLE VII

PATIENTS TEMPORARILY IMPROVED, NOT FREE FROM ATTACKS

SERIES NO.	NAME	SEX	H.L.H. NO.	CHARACTER OF ATTACK	FREQUENCY	AGE AT ONSET	AGE WHEN DIET WAS BEGUN (YR.)	DURATION BEFORE KETOGENIC TREATMENT (YR.)	PREVIOUS TREATMENT RESULTS	PRELIMINARY STARVATION (DAYS)	ADDITIONAL TREATMENT AT TIME OF IMPROVEMENT	INTERVAL BEFORE IMPROVEMENT (MO.)	TIME ON 4:1 DIET (MO.)	TIME BEFORE NORMAL DIET RESUMED (MO.)	DURATION OF IMPROVEMENT (MO.)	STATUS OF TREATMENT AT TIME OF IMPROVEMENT	STATUS OF TREATMENT AT TIME OF RELAPSE
13	K. H.	F.	50597	Petit mal 4 grand mal	25-50 daily	7	13½	6½	Ph. Br. Dehydration. No improvement Salicylates, Theobromine temporary improvement	6	Theobromine	0	7	8	3	4:1 Good ketosis	4:1 Good ketosis
14	E. R.	F.	55734	Minor motor	15-25 daily	5½	8½	3	0	6	NH_4Cl Theobromine	0	20	20	15	4:1 Good ketosis	4:1 Good ketosis
15	R. S.	M.	21918	Grand mal	5-6 daily	6	15½	9½	Ph. Br. No improvement	0	Ph. 3.0 gr.	1	6?	8	5	4.5:1? Ketosis variable	Breaking diet, poor ketosis

PATIENTS WHO SHOWED SOME TEMPORARY IMPROVEMENT BUT DID NOT BECOME FREE FROM ATTACKS

There were three instances (Table VII) in which the course of the disease seemed to be influenced favorably for a short period after the institution of the diet. These patients did not have remissions. Subsequently the disease became as severe as before treatment.

CASE 13.—K. H. (H.L.H. No. 50597), female, aged thirteen and one-half years at time of treatment. Idiopathic epilepsy. I. Q. was 76. Petit mal attacks and occasional convulsions. Onset was at seven years. Phenobarbital, bromides, pyramidon, and fluid restriction had proved of no value. Salicylates and theobromine had caused some temporary improvement. At time of ketogenic treatment she was having twenty-five to fifty petit mal attacks daily. The institution of the diet caused the petit mal attacks to stop for three months, although three convulsions occurred during this interval. After this short period, the disease became, if anything, more severe than before treatment. Cooperation had been good.

CASE 14.—E. R. (H.L.H. No. 55734), female, aged eight and one-half years at time of treatment. Idiopathic epilepsy. Slight mental retardation. Minor motor attacks. Onset was at the age of five and one-half years. For the first fifteen months after the beginning of the diet, the attacks were reduced from fifteen to twenty-five to one to three daily. At the end of this time, without any apparent cause, the attacks returned to their former frequency and became more violent. Cooperation had been good throughout treatment.

CASE 15.—R. S. (H.L.H. No. 21918), male, aged fifteen and one-half years at time of treatment. Idiopathic epilepsy. Slight mental retardation. Onset was at 6 years. Frequent and severe generalized convulsions with periods of status epilepticus. At time of treatment he was having five or six severe attacks daily and was dull and incapacitated most of the time. Phenobarbital and bromides had been ineffectual over a five-month period. There seemed to be gradual improvement with finally freedom from seizures for four weeks when he was treated with a 4.5:1 diet and 3 gr. of phenobarbital. A severe relapse into violent status epilepticus occurred at a time when the diet was being broken and phenobarbital decreased. Whether there would have been continued improvement with better cooperation cannot be determined.

CASES SHOWING NO EFFECTS FROM KETOGENIC DIET

The fifteen cases which showed no response to ketogenic therapy are summarized in Table VIII. Two of these patients (Cases 16 and 18) had seizures exclusively of the grand mal type. Six (Cases 17, 19, 21, 26, 28, and 29) had seizures exhibiting minor motor manifestations, four (Cases 22, 23, 24, and 27) were subject only to typical petit mal attacks without any motor manifestations, and three (Cases 20, 25, and 30) had predominantly petit mal attacks with only occasional convulsions. These children were all over seven years of age, except one (Case 29). In six instances (Cases 19, 21, 22, 25, 26, and 27) the disease was of less than three years' duration at the time of treatment, and in four (Cases 21, 22, 25, and 26) of these cases less than eighteen months. The remaining eight children had been subject to seizures for five to thirteen years.

TABLE VIII

PATIENTS NOT IMPROVED

SERIES NO.	NAME	SEX	H.L.H. NO.	CHARACTER OF ATTACK	FREQUENCY	AGE AT ONSET	AGE WHEN DIET WAS BEGUN (YR.)	DURATION BEFORE KETOGENIC TREATMENT	PRELIMINARY STARVATION (DAYS)	RESULTS OF STARVATION	ADDITIONAL TREATMENT	DURATION OF DIET	KETOSIS
16	E. G.	F.	49766	Grand mal	Daily-weekly	2 mo.	8	8 yr.	0		Ph. NH_4 Br. Theobromine NH_4Cl Dehydration	5 mo.	Good
17	G. H.	F.	60642	Minor motor Grand mal	Weekly-monthly Quarterly-yearly	18 mo.	9	7½ yr.	0		0	13 mo.	Good
18	C. J.	F.	70229	Grand mal	Daily-weekly	10 mo.	14	13 yr.	6	Free 11 days	Ph. Pr. Btr.	9 mo.	Good
19	N. L.	F.	65704	Minor motor	Daily	8 yr.	10	2 yr.	3	Not improved	Ph.	8 mo.	Good
20	P. M.	M.	55155	Petit mal 2 grand mal	25-50 daily	14 mo.	7	6 yr.	3	Slightly improved	None, worse with drugs	3 mo.	Good
21	R. P.	F.	74324	Minor motor	30-60 daily	7 yr.	7½	8 mo.	5	Free 7 days	None, worse with Ph.	4½ mo.	Good
22	M. S.	F.	61306	Petit mal	12 daily	9½ yr.	10½	1 yr.	5	Not improved	Theobromine	12 mo.	Good

TABLE VIII—CONT'D

SERIES NO.	NAME	SEX	H.L.H. NO.	CHARACTER OF ATTACK	FREQUENCY	AGE AT ONSET	AGE WHEN DIET WAS BEGUN (YR.)	DURATION BEFORE KETOGENIC TREATMENT	PRELIMINARY STARVATION (DAYS)	RESULTS OF STARVATION	ADDITIONAL TREATMENT	DURATION OF DIET	KETOSIS
23	E. W.	F.	56491	Petit mal	3-40 daily	9 yr.	14	5 yr.	5	Free 14 days	NH_4Cl, Theobromine	7 mo.	Good
24	I. C.	F.	63094	Petit mal	30-100 daily	3½ yr.	12	8½ yr.	7	Free 10 days	NH_4Cl, Ph.	1 mo.	Slight
25	F. F.	F.	44944	Petit mal and minor motor 3 grand mal	4-5 daily	12 yr.	13½	1½ yr.	3	Not improved	Ph. Pr.	8½ mo.	Good
26	W. C.	M.	Pvt. pt.	Minor motor	1-3 daily	8½ yr.	9	5 mo.	5	Free 11 days	Ph. Br.	16 mo.	Good—6 mo
27	J. C.	F.	64681	Petit mal	10-15 daily	8½ yr.	10	1½ yr.	4	Free 11 days	0	2 wk.	Slight
28	M. H.	F.	72314	Minor motor	15-20 daily	6 yr.	15	9 yr.	7	Slightly improved	0	9 days	Good
29	J. H.	M.	85341	Minor motor	4-100 daily	10 mo.	4½	3½ yr.	5	Slightly improved	Mebaral	14 mo.	Good
30	W. F.	M.	37622	Petit mal occasional Grand mal	1-6 daily occasional status	5 yr.	11	6 yr.	5	Free 14 days	Ph. Br. Btr. Air injection	5 mo.	Good

In thirteen cases, the diet was preceded by a preliminary period of starvation—usually lasting three to five days. It is of interest that in seven of these thirteen cases the attacks stopped during the starvation period only to return within two to fourteen days after the diet was begun. In three instances starvation exerted no influence, and in the other three cases there was only slight improvement. There were two children (Cases 24 and 27) who could not be maintained in ketosis by a 4:1 diet, even though they cooperated thoroughly.

The treatment was carried out just as intensively in these cases as in the other groups which responded better. In all instances the diet was started in the hospital. Many of the children remained in the hospital for a number of months. Their cooperation was good both in the hospital and after returning home. The diet was continued for three to sixteen months, in all except two instances. In combination with the ketogenic diet, various other types of therapy were tried in most instances. The psychologic side was not neglected and environmental adjustments were made. Phenobarbital, prominal, mebaral, and bromides were used in many cases. The production of acidosis by means of NH_4Cl was tried in some instances. The reduction of body fluids by means of periods of starvation, restriction of fluid intake, low salt diets, and the administration of theobromine sodium salicylate was used as adjuncts to ketosis in many of the cases. After a careful review of these cases, we must admit that none of these patients showed any benefit which could be attributed to the ketogenic diet.

DISCUSSION

Of thirty patients treated, eight, or 26.6 per cent, have remained free from attacks for long periods and have resumed an unrestricted diet. Four patients had temporary remissions of considerable duration but relapsed to their previous condition. In three other cases the disease was influenced favorably for a period but the attacks did not stop. In the seven instances in which the attacks did not stop permanently, the continued maintenance of the diet was not considered worth while. Fifteen patients (or 50 per cent) were not benefited.

The group that we have studied is too small to be of much value. It is true that remissions have been encountered by the writer[10] and by Lennox[12] and Turner[11] in 19 to 24 per cent of epilepties who were either not treated or were treated by methods other than the ketogenic diet. The incidence of remissions in our patients under ketogenic therapy is not much better than this. On the whole, the treatment may be considered to have had some degree of success because almost all these patients had severe forms of epilepsy with numerous and frequent attacks and many of them were suffering from the petit mal type. The expectancy of remission in these patients was considerably less than the average.

In comparing the patients whose attacks have stopped with those who were not benefited by the ketogenic diet, it is seen that seven of the eight patients of the former group had been subject to the disorder for less than three years, whereas only six of the fifteen patients not benefited had had attacks for less than three years. This may be of significance in the prognosis for success.

A review of the histories of the patients successfully treated, in an attempt to determine whether the ketogenic diet was directly responsible for the outcome, often leaves one in doubt. In certain instances the diet appears to have immediately and definitely influenced the course of the disease and eventually to have controlled the attacks. How it could have permanently altered the neurophysiologic mechanism so that attacks did not recur after the diet was discontinued is a mystery. In other cases the relationship of the dietary therapy to the favorable outcome is more obscure, since in some of these the attacks stopped at the very time that the patient was breaking the diet and that ketosis was poorly maintained. The use of sedative drugs in addition to the diet has also obscured the interpretation. Finally the fact that remissions, or even permanent cures, are sometimes encountered in patients with even the most severe forms of epilepsy, who are not receiving any treatment, makes one hesitate to evaluate any therapeutic measures in a particular case.

In spite of our inability to evaluate scientifically the results obtained with the ketogenic diet, we believe that the favorable results sometimes encountered in cases of a type most unresponsive to other therapeutic measures justify its trial whenever attacks remain uncontrolled by sedatives.

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A CASE OF RATBITE FEVER WITH DEMONSTRATION OF SPIRILLUM MINUS

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ALTHOUGH the etiologic agent of ratbite fever has been known since 1916,[1] all 13 of the laboratory proved cases in the United States have been reported within the last eleven years. In eight of these cases[2-8] *Spirillum minus* was found by the inoculation of animals (mice, rats, guinea pigs) with blood, inflamed tissue, or exudate from the patient; in 3 cases[9-11] by direct dark-field examination of serum from the primary lesion, from a lymph node, or from a secondary skin macule, and in one case by dark-field examination of the patient's venous blood.[12] In the thirteenth case (Case 81 cited by Bayne-Jones[13]) the spirillum was reported as found in blood culture. In an additional case report[14] the laboratory diagnosis is made doubtful by the fact that only a single spiral organism was seen in the blood of the inoculated guinea pig.

The following case of ratbite fever is being presented for two reasons: first, that, of over 80 cases of the disease reported from 23 of the states,[13] only the above cited thirteen had the diagnoses proved by the demonstration of the causative spirillum; and, second, that no authentic case has yet been reported from Kentucky,[15] that of Orr[16] from this state being unproved, and not typically responsive to arsphenamine treatment.

CASE REPORT

A three-year-old white girl was admitted to Children's Free Hospital in Louisville on Nov. 19, 1934, with a provisional diagnosis of ratbite fever. Five weeks previously, she had been bitten on the right hand by a rat. Two days later the hand became swollen and painful, and the corresponding axilla was sore, but the inflammation subsided within a week under local treatment. Four weeks after the bite there was sudden fever, and round, red blotches appeared on the body. In twenty-four hours both fever and eruption were gone. Three days later they recurred, and she was brought to the hospital.

On admission she was noted as well nourished and not seriously ill. Her temperature was 101° F., pulse 124, respiration 24. The skin of the body and limbs was blotched with a purple red, maculopapular rash, whose spots ranged in diameter from 1 or 2 to 20 mm. and disappeared on pressure. The rest of the physical examination was negative, except for a small scar at the site of the bite.

Laboratory.—The blood count on entry was red blood cells, 3,400,000; hemoglobin, 80 per cent; white blood cells, 8,850, with neutrophiles 58 per cent, lymphocytes 41

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per cent, and basophiles 1 per cent. A urinalysis was negative. The blood Wassermann and Kahn tests were negative three days after admittance, but on Jan. 3, 1935, the Wassermann test was reported plus-minus, and on February 1, two-plus, the Kahn remaining negative.

Course.—On her third day in the hospital, the patient's temperature rose to 105° F., and a rash like the earlier one appeared. Again, both fever and rash disappeared within twenty-four hours.

Three days later, as her temperature was rising in the fourth attack, she received 0.1 gram of sulpharsphenamine intramuscularly. The rash did not reappear.

Treatment was continued for six 0.2 gm. doses of sulpharsphenamine at biweekly intervals, and neither rash nor fever has recurred.

The scar of the wound did not appear inflamed at any time during her hospital stay, and no lymph node enlargement was found.

Diagnosis.—When the temperature was 105° F., in the third accession, 4 c.c. of blood were taken from a cubital vein, and 2 c.c. were injected immediately into the peritoneal cavity of each of two white mice.

Ten days after these injections dark-field examination of the blood of the mice failed to show any spirilla. Twenty days after injection the blood of both mice upon dark-field examination was found to contain numerous, short, quick-darting, undulate organisms, exactly suiting descriptions and photographs of *Spirillum minus.*

The mice showed no external evidence of sickness, except a transitory ruffling of the hair. Their blood continued to show spirilla for several weeks, after which time no further examinations were made.

In searching the dark-field preparations for spirilla, it was observed that often for the first hour after the drop of blood was placed on the slide no spirilla could be found; then they would begin to appear, shooting to and fro in the spaces among the red cells. In addition to the spirilla, several other moving bodies were seen, which might possibly cause confusion in diagnosis, if misinterpreted. The first of these was a motile bacterium which appeared in the preparations after an hour or two. The second was a very fine, wavy, scintillant filament which was seen attached to red cells and fluttering in currents in the plasma. The third, which may lead to a probably erroneous conclusion that the spirillum has an intracellular phase, was a small, refractile, rapidly moving particle seen inside the red cells, especially if hemolysis had been produced by adding distilled water to the preparation. Both of the last two objects are seen in normal mouse blood. A fourth possibility of error, not encountered in the above case, is the occurrence of spirilla in the blood of the mouse before inoculation. For this reason a negative examination, preceding the positives, is important as a control.

COMMENT

The method used above for demonstrating *Spirillum minus,* i.e., the intraperitoneal inoculation of animals (of which the white mouse is best) with venous blood, taken at the height of the fever (or with fluid from a lymph node or primary or secondary skin lesion), and the subsequent search for the organism in the animal's blood has been

found by the majority of observers to be the most certain. The least satisfactory way is the direct searching of the patient's blood, there being in the entire literature only three accounts of success by this method.[12, 17, 18] Cultivation of *Spirillum minus* on artificial media has not been proved possible.[13, 19, 20]

The clinical features of the above case and the appearance of the observed organism conform well to the descriptions and illustrations given by McDermott,[19] Schockaert,[20] Robertson,[21] and Francis[22] in their monographs.

SUMMARY

The cases of ratbite fever in the United States are reviewed in which *Spirillum minus* was demonstrated, and another such case is reported.

The methods of laboratory diagnosis are briefly discussed.

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LATE RESULTS OF TREATED CHILDHOOD HYPOTHYROIDISM

Two Case Reports

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WHILE many reports are available describing the original status of children with hypothyroidism—Gordon[3] in 1922 reviewed 340 cases chronicled in North America alone—relatively few are to be found in which their progress and status after long periods of treatment with thyroid substances are described.

Among the more complete records of longer followed juvenile cases are 13 reported by Nobel,[5] 11 by Tow,[9] and one each by Canelo and Lisser,[2] Kerley,[6] Price,[7] and Zuber.[10] Observation periods range from two to thirty-one years. All reports show great variation in the end-results when measured by such criteria as appearance, height, weight, and intelligence. Bone age is recorded by Canelo and Lisser, Nobel, and Zuber.

Two additional cases are here presented, in both of which serial data at successive age levels are available for most of the important developmental factors. In both, symptoms of myxedema were noted at an early age (one year and two months, respectively) and treatment at the time this report was compiled had continued for fourteen years and ten years, respectively.

Case 1.—*Status on Entry:* R. R., female, born Dec. 3, 1917, was first seen at the age of three years eleven months in Lane Clinic on Nov. 12, 1921, with the complaint of recurrent sores since birth. The patient was the youngest of eight children, the others being alive and well. The patient was born and had lived in the Santa Clara Valley, Calif. The prenatal and the birth history were normal, the birth weight being 7.5 pounds. The baby was breast fed for two months, then put on cow's milk formulas. Progress was satisfactory, the child sitting up at six months and cutting the first tooth at nine months (sisters and brothers all cut first teeth at this age). At twelve months she could stand up and speak a word or so.

In 1918, at the time of the pandemic, she had what was purported to be influenza. During the next three years the child became obstinately constipated and lost her appetite. Development seemed to be stationary. She neither walked nor talked and appeared "sluggish and backward" to the mother. Also during this period the child had a persistent large umbilical hernia and frequent attacks of what was probably impetigo. She was brought to the clinic because of the impetigo and seeming lack of development.

Physical examination in November, 1921, revealed a dull appearing girl who was far below par in height and weight. The face showed well-marked nasolabial and

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mentolabial sulci and deep superorbital folds. The peculiar appearance seemed dependent upon an increased thickness of the skin and subcutaneous tissue. The lips were thick. There were 20 teeth, and the tongue appeared normal. The hair was moderately thick and coarse. Heart and lungs were negative. The abdomen was protuberant, and a large umbilical hernia was present. The skin was coarse, dry, and somewhat thickened, and the subcutaneous tissue was dense and boggy. The legs presented a moderate degree of genu varus. Some impetigo was noted over the face and body.

Measurements taken on the first and succeeding entrances are compared on the growth curve and development chart.

Laboratory work revealed a moderate secondary anemia and a negative blood Wassermann reaction. X-ray studies gave a bone age of one year. The mental retardation was evidenced by the failure to walk and talk.

A diagnosis of thyroid deficiency was made. From the history, it seemed apparent that the condition, in spite of its severity, did not come on until approximately one year of age. This would coincide with the testimony of the bony status.

Medication and Basal Metabolic Rates.—The records of thyroid dosage are somewhat incomplete. R. R. lived out of town and was seen only at long intervals. She was started immediately in November, 1921, on 1 grain (Burroughs and Wellcome) daily, and this dose was increased to 3 grains daily within the first two months. She was kept at this dosage for three years, but some time during the next six years it was raised by an out-of-town physician to 5 grains daily. In August, 1930, when she was seen again at the hospital, she showed evidence of a mild thyrotoxicosis. At this time she was placed on ½ grain (Armour) daily. When she came in again in November, 1935, the dose was still the same and seemed to be adequate.

The measurement of oxygen consumption was never used as a guide to dosage, but determinations of the basal metabolic rate have been made at intervals. Following Talbot's suggestions[8] the actual calories for twenty-four hours are given in Table I, together with percentage readings calculated against Talbot's weight standards, his height standards, and the Boothby-Sandiford standards.

TABLE I

PATIENT R. R.

DATE	AGE (YR.-MO.)	HEIGHT (C.M.)	WEIGHT (KG.)	CALORIES PER 24 HR.	BASAL METABOLIC RATE		
					TALBOT HEIGHT STANDARD	TALBOT WEIGHT STANDARD	BOOTHBY-SANDIFORD STANDARD
1/14/24	6- 1	95.8	15.4	1015.2	+43	+39	+45
8/22/30	12- 9	132.1	31.3	1312.8	+29	+21	+36
11/ 9/35	17-11	151.0	41.2	988.8	-24	-22	- 7

Photographs.—The photographs are not taken to scale; they are shown, therefore, only to illustrate development and change in body type.

The first of the set of R. R. (Fig. 1) was taken before treatment was instituted. It appears to be an almost classical example of thyroid deficiency. Two months later the child, although still looking much younger than her forty-nine months, is remarkably improved (Fig. 2). By fourteen years the photograph suggests no abnormality except a delayed adolescence (Fig. 3); by eighteen years the picture seems to show a fully developed young woman with a quite delicate face (Fig. 4). As it stands the picture gives no hint of the early hypothyroid state, although the evidence of this is still carried in the shortness of stature and mental handicap, which are demonstrated in the other charts. Menarche occurred at the age of thirteen years, with normal menses subsequently.

Fig. 1. Fig. 2.

Fig. 1.—R. R., Nov. 12, 1921; aged three years eleven months.
Fig. 2.—R. R., Jan. 13, 1922; aged four years one month.

Fig. 3. Fig. 4.

Fig. 3.—R. R., Dec. 1, 1931; aged fourteen years.
Fig. 4.—R. R., Nov. 11, 1935; aged seventeen years eleven months.

Anthropometric Measurements and Graphic Growth Records.—Data on height and weight are plotted on the graphic growth record[1] (Fig. 5). The graph shows R. R. to have a definite height retardation, but of decreasing degree throughout; her weight is about average for her height except that at six years she was relatively more plump than before or after.

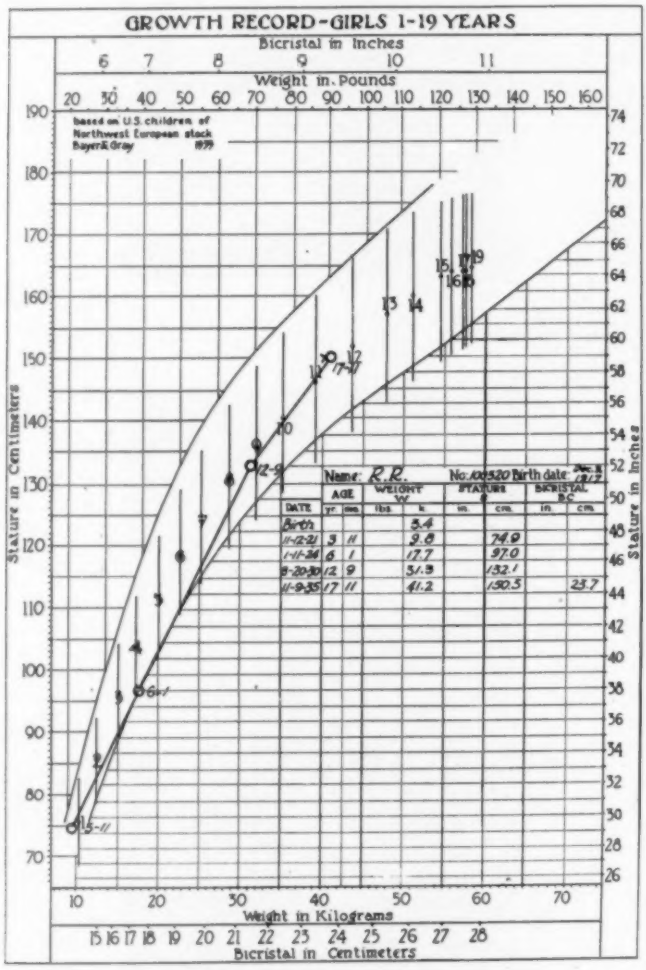

Fig. 5.—R. R. Growth curve.

More extensive anthropometric measurements made at the last visit confirm the clinical and photographic impressions.

The developmental charts are an attempt to summarize the data on bone age and mental age graphically. Height is shown again, calculated this time as height age, in order to contrast growth and development factors on the same screen.

The points for the graphs are calculated on the principle made familiar by the concept of the intelligence quotient. Any given finding, as height, bone development, or mental development, was first converted into age. For height this was done by reading against a mean height-age curve for girls calculated from the same data of Gray and Ayres[4] which served as a basis for graphic growth records. For osseous development this was done by reading as far as possible against Todd's standards; when these were not applicable, the standards of Engelbach and McMahon were used. The mental age was scored by the usual mental tests.

To convert these various development ages into development quotients, they were converted into months and divided by chronologic age, at the moment, also in months. The resultant percentage is plotted on the graph.

It is necessary to emphasize that although 100 per cent is the line of the mean, still for every factor a characteristic variation in percentage above and below the mean is well within normal limits. For height, for instance, the variation which includes 96 per cent of normal children is about ±8 per cent. This must be kept in mind in interpreting the charts.

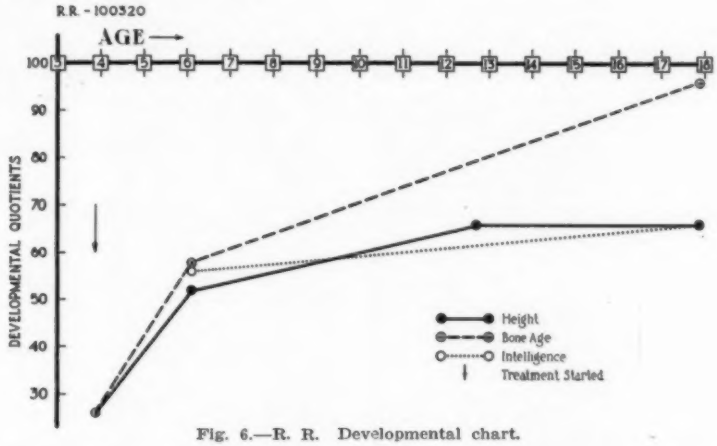

Fig. 6.—R. R. Developmental chart.

From R. R.'s chart (Fig. 6) it is apparent that her growth (height) and bony development were retarded to a like high degree at the first observation, being only 25 per cent of the mean. They stayed fairly well together for the second set of observations, when a first test showed the mental development to be also on a par with the physical measures. From then on her stature and mental age stayed together, whereas ossification proceeded normally, so that now, at age seventeen years eleven months, her epiphyses are closed, and she is not to be expected to enjoy any significant growth. With height still only at 60 per cent of normal, she is therefore permanently dwarfed.

CASE 2.—*Status on Entry:* E. G. was born Dec. 17, 1924, also in California. She was first brought into the clinic on Oct. 20, 1926 (aged twenty-two months), because of slow teething, increasing overweight, and sluggish reactions to people and things.

There was no endocrine abnormality in the family; there were no siblings. Parental and natal records were not remarkable, and the baby was breast fed for ten months. The first tooth, however, was not cut until fifteen months, at which time walking began also. Known weights were 8 pounds at birth; 21 pounds at ten months; 27.5 pounds on entry. Except for the retardation in development she had been remarkably well.

Examination on entry showed a child who was below the lower limits of normal height for her age and above the weight range for her height. In appearance she suggested the hypothyroid state with fat pads on back, pudgy hands, broad face, flat nose, large tongue, and pot belly. The skin was dry and hair coarse. Only 6 teeth were present, 2 lower central and 4 upper incisors. Blood and urine were normal, but the x-ray films of the wrist showed a bone age of only two months. The mental age was not measured, but there was an obvious retardation in that the child had very slow reactions and failed to respond to the presence of her parents.

A diagnosis of hypothyroidism was made. Although the history of onset was not clear cut, the greatly delayed bone age suggests that it could not have been later than the early months of postnatal life.

Medication and Basal Metabolic Rates.—On her first visit in October, 1926, E. G. was given ¼ grain of thyroid extract (Burroughs and Wellcome) daily. By January, 1927, this was increased to ¾ grain daily and kept at this level through the year. In January, 1928, she was changed permanently to Armour's preparations and has remained on a daily dosage between ½ grain and 1 grain daily, except for two intervals: the first gap was experimental—for a period of two months from September to November, 1930, after which interval her basal metabolic rate was lower, and she seemed much less active. The other interval was a careless lapse of one month in September, 1935, after which the basal metabolic rate was very low, and the child seemed sluggish. Since then she has been taking 1 grain daily. More than this leads to tachycardia almost constantly above 100.

The calories per twenty-four hours and the basal metabolic readings, again calculated according to the three standards, are given in Table II.

TABLE II

PATIENT E. G.

DATE	AGE YR.MO.	HEIGHT CM.	WEIGHT KG.	CALORIES PER 24 HR.	BASAL METABOLIC RATE		
					TALBOT HEIGHT STANDARD	TALBOT WEIGHT STANDARD	BOOTHBY-SANDIFORD STANDARD
7/11/30	5- 7	108.0	21.8	1084.8	+37	+22	+ 6
11/ 6/30	5-11	109.2	22.7	818.4	+ 2	-10	-20
8/ 3/32	7- 8	121.0	27.0	991.2	+10	-12	-11
2/ 6/33	8- 2	124.2	28.1	1132.8	+21	+10	+ 1
11/29/35	11-11	142.4	42.7	916.8	-21	-28	-33

Photographs.—The collection on E. G. (Figs. 7, 8, 9, and 10) are less striking in themselves, partly because the two early ones are home snapshots taken with the child dressed. However, the series makes a good contrast with those of R. R., because it is apparent that no such transformation occurs here as went on in the other girl. The child is shown throughout to be a broad, chubby, smiling youngster. At the beginning, she had fewer stigmata of thyroid deficiency in her physical appearance than in other phases of her development, especially bone development, whereas today, when other factors are quite fully compensated, her barrel body and broad face still suggest the hypothyroid state.

Anthropometric Measurements and Graphic Growth Record.—Complete anthropometric measurements have been recorded at yearly intervals for four years. They show the child to be taller and heavier set than R. R., the only definite abnormality being a very high nasal index, i.e., her nose is too short and too wide.

When the values for height, weight, and pelvic breadth are transferred to the growth graph (Fig. 11) it is apparent that there is a height retardation of decreasing degree, which was never as marked as R. R.'s. From her fourth year on she is always within normal stature range, and at present, in fact, well toward the middle

Fig. 7.

Fig. 8.

Fig. 7.—E. G., aged approximately one year four months.
Fig. 8.—E. G., aged approximately two years four months.

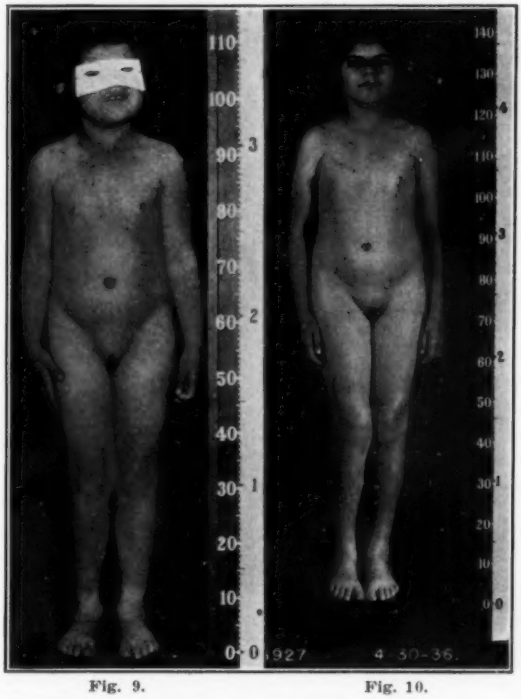

Fig. 9.

Fig. 10.

Fig. 9.—E. G., Dec. 14, 1931; aged seven years.
Fig. 10.—E. G., March 30, 1936; aged eleven years four months.

of it. Her weight is always on the heavy side of the mean, and generally at the upper border of normal. Her bicristal diameter is also on the broad side of the average, but normal.

Developmental Chart.—E. G.'s chart (Fig. 12) shows some interesting contrasts and similarities to that of R. R. Neither growth nor mentality was ever so much re-

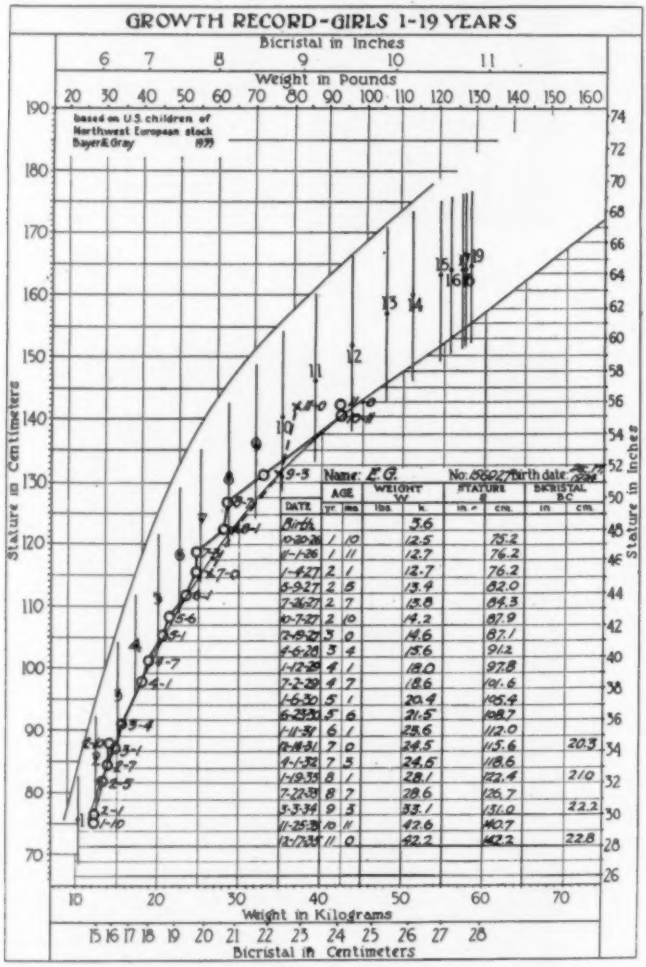

Fig. 11.—E. G. Growth curve.

tarded, whether one compares original figures, or figures at similar chronologic levels. Bone age, on the contrary, was more retarded at the beginning. Mental development was actually precocious after the fourth year, but at the age of eleven years, all three factors are comfortably near the 100 per cent line. She is now a normal girl with every expectation of attaining her full genetic development and stature.

SUMMARY

1. The original status and progress of two children with thyroid deficiency, onset approximately at one year and two months, respectively, are presented. They have been followed, under treatment from approximate ages of four to eighteen years, and two to eleven years.

2. Both children had at the beginning the appearance and build characteristic of thyroid deficiency and a significant retardation in height, bony development, and mental development.

3. The most striking similarity in the two records is the complete restitution of osseus development in both children. This finding is in agreement with the results of other authors. Canelo and Lisser and Price record significant advances in bone age under treatment; similarly 9 out of 13 of Nobel's patients had normal bone ages at the end of the observation period.

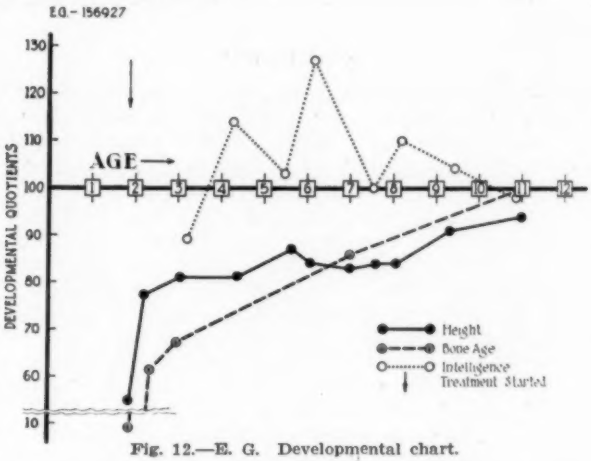

Fig. 12.—E. G. Developmental chart.

4. Contrasts between the two are: the older girl has developed a nicely proportioned body with quite a delicate face, but she has remained permanently dwarfed, and her intellect has not developed beyond the ten-year six-month level. The younger one, on the other hand, has retained her thick-set build but has compensated completely in height and mentality.

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ATRESIA OF THE PULMONARY ORIFICE WITH INTACT INTERVENTRICULAR SEPTUM

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ATRESIA of the pulmonary orifice without an interventricular septal defect is a comparatively rare anomaly. In her survey of 850 cases of congenital cardiac malformations, Abbott[1] lists 7 such instances. Recently, such an anomaly has been observed in this laboratory. In this case, in addition to the atresia of the pulmonary orifice with intact interventricular septum and patent foramen ovale and ductus arteriosus, there was a congenital hydronephrosis, umbilical hernia, and absence of the auricles with atresia of the external auditory canals.

CASE REPORT

The mother, a seventeen-year-old negress, was admitted to the Jewish Hospital of Brooklyn, on July 6, 1936, complaining of "rupture of membranes." She stated that this was her second pregnancy and that the first child, delivered at term, was alive and well. Her last menstrual period began on Nov. 1, 1935. On admission, the fetal heart sounds were audible, and the presenting part, the vertex, was floating. The membranes were intact, and there was a large polyhydramnios. The Kline test was negative. Roentgenographic examination revealed no abnormalities of the pelvis or fetus. On July 13, 1936, at 10:40 A.M., labor was induced by artificial rupture of the membranes, following which the fetal heart sounds became inaudible. On the same day at 2:45 P.M. she was delivered of a dead male child.

At necropsy the newborn weighed 2,500 gm. and was 41 cm. long. The mucous membranes and the skin of the head, face, neck, and chest were deep purple. The head was well formed. Both auricles were absent; a dimple of the skin marked the site of each external auditory canal. The chest was well shaped. There was an umbilical hernia, devoid of skin covering, protruding 6 cm. above the surface, through a defect in the anterior abdominal wall 8 by 8 cm. in diameter. Through the transparent wall of the hernia, portions of the small intestine and liver were visible. In addition, fetal atelectasis of the lungs, congenital bilateral hydronephrosis and hydroureter, and undescended testicles were observed.

Description of the Heart.—In situ the heart appeared enlarged and globular. It measured 3.5 cm. from apex to base and 5 cm. across the base. The apex was rounded and was composed entirely of the left ventricle (Fig. 1, *A*). The pulmonary artery and aorta arose in the usual manner, measuring 0.5 and 1.3 cm. in circumference, respectively. The disposition of the coronary sinus and its tributaries, the superior vena cava, and the inferior vena cava was not unusual.

The right atrium was markedly dilated and formed the right border of the heart. The wall measured 0.2 cm. in thickness; the endocardium was smooth and glistening. The right atrioventricular orifice measured 2.8 cm. in circumference; the leaflets of the tricuspid valve, as well as the chordae tendineae, were delicate and well formed. The wall of the right ventricle was 0.6 cm. thick. The cavity of the right ventricle was diminutive, measuring 0.5 by 0.3 by 0.3 cm. (Fig. 1, *B*).

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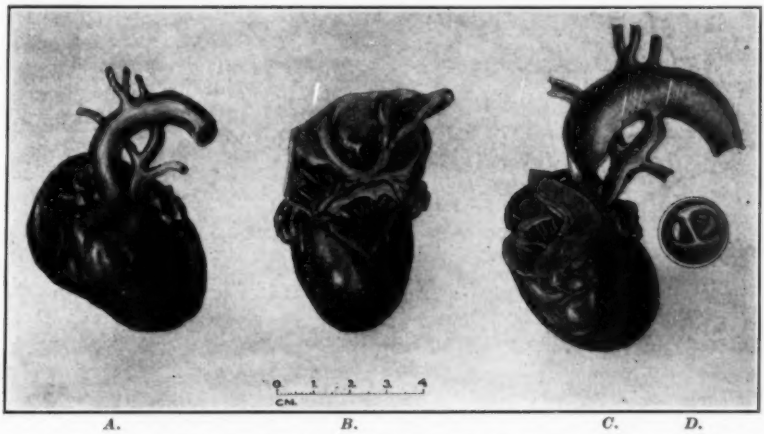
The pulmonary orifice was obliterated by fusion and thickening of the semilunar valves (Fig. 1, *C* and *D*). The conus arteriosus was narrow and directly continuous with the cavity of the ventricle. The pulmonary artery was small, its wall thin, and its intimal surface smooth and glistening. After a course of 1.2 cm. it divided into the right and left branches and continued as the ductus arteriosus. The opening of this into the aorta measured 0.3 cm. in diameter.

The left atrium was somewhat dilated. A thin, netlike septum partially covered the foramen ovale, allowing an aperture 1.5 by 0.5 cm. in diameter. The left atrioventricular orifice measured 3.3 cm. in circumference; the leaflets and chordae tendineae of the mitral valve were well formed and delicate. The trabeculae carneae were flattened. The wall of the left ventricle measured 0.6 cm. in thickness. The interventricular septum was intact; its membranous portion was translucent. The valves of the aortic orifice were well formed and delicate. The right coronary artery arose from the right sinus of Valsalva, and the left from the left sinus. The course of the coronary arteries and their branches was not unusual. Two and one-half centimeters from the bulbus of the aorta there arose a vessel which divided



A. *B.* *C.* *D.*

Fig. 1.—Atresia of the pulmonary orifice with intact interventricular septum in a negro stillborn. The right atrium is markedly dilated and forms the right border of the heart. The pulmonary artery is small. The foramen ovale is open. The cavity of the right ventricle is diminutive. The interventricular septum is intact. The pulmonary orifice is obliterated by fusion and thickening of the semilunar valves. A view of the pulmonary orifice from above is shown magnified 3 times (*D*).

into the innominate and left common carotid arteries; the left subclavian artery arose in the usual manner. The distribution of the main branches of these vessels presented nothing remarkable.

COMMENT

According to Peacock,[2] it was Hunter (1783) who first described a case of pulmonary atresia with intact interventricular septum. A male child, born at the eighth month, had marked cyanosis and violent palpitation, and died in convulsions on the thirteenth day. Hunter gave the following description: "The pulmonary artery at its beginning from the right ventricle was contracted into a solid cord and was completely impervious, but the trunk was open, though small. The foramen ovale was very large. The ductus arteriosus was open

and resembled a branch from the aorta, and furnished a scanty supply to the pulmonary arteries. It arose immediately opposite the left subclavian artery. The right ventricle had scarcely any cavity, and the auriculoventricular aperture was especially small. The left ventricle was large and powerful."[3]

Subsequently, similar cases were reported by Lordat and Dalmos[4] (1822), Hall and Vrolik[5] (1825), Hare[6] (1852), Rokitansky[7] (1855), Ollivier[8] (1861), and Gueniot[9] (1861). In presenting a case of his own, Peacock (1869), quoted all the above cases. The child he observed lived nine days. He found the orifice of the pulmonary artery obstructed by adhesions of the cusps. On the arterial side three ridges and corresponding depressions were seen. The trunk of the pulmonary artery was somewhat small and narrow. The foramen ovale and ductus arteriosus were open. The cavity of the right ventricle was small, that of the left was large, and its wall was thickened. The aorta arose in the usual manner.

Rauchfuss[10] (1878), collected 192 cases of anomalies of the pulmonary artery. There were 21 with intact interventricular septum, and of these 10 had atresia of the pulmonary orifice. Subsequently, Thérémin[11] (1895) and Vierordt[12] (1898) each collected and classified 10 cases of atresia of the pulmonary orifice with intact interventricular septum. These authors do not describe any cases in detail or designate whether they include the cases previously reported. They group them according to the position of the atresia, the state of the cardiac orifices, and the condition of the ventricles. While alive the patients presented varying degrees of cyanosis and dyspnea; their life spans were short.

Abbott (1927) includes 7 cases in her series. The anatomic findings in these are essentially the same as in those reported earlier in the literature.

According to Abbott and her coworkers,[13] "Pulmonary stenosis or atresia with closed interventricular septum is of unusual occurrence and is due to fetal endocarditis setting in after the heart has formed." While this may be true, it is difficult to produce and evaluate the evidence supporting this view. In any event, the case here presented and those reported by others suggest that either the atresia of the pulmonary orifice occurred subsequent to the completion of the interventricular septum, or that a compensatory mechanism for sufficient function of the heart was established which obviated the necessity for patency of the septum.

SUMMARY

The unusual cardiac anomaly, atresia of the pulmonary orifice with intact interventricular septum, is described in a stillborn negro infant who also had bilateral hydronephrosis, umbilical hernia, and absence of the auricles with atresia of the external auditory canals.

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PROGRESSIVE FACIAL HEMIATROPHY

Report of Two Cases With Cerebral Calcification

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THIS report deals with two cases in which progressive facial hemiatrophy and cerebral calcification were observed together in a girl twelve years old and in a boy fifteen years old. As far as we know, such an association has not been reported heretofore.

Archambault and Fromm[1] stated that progressive facial hemiatrophy was definitely a disease of early life, particularly of the second decade, but that cases have had their onset in the first years of life, some of them having been apparently congenital or due to birth trauma. In spite of this statement, comparatively few cases in children have been reported, although many of the adults with progressive facial hemiatrophy have given histories of a lesion which dated back to their childhood.

As an excellent bibliography of reports up to 1930 has been given by Archambault and Fromm,[1] a summary of the literature since 1930 only has been included at the end of this paper. The total number of cases reported up to 1936 is approximately 440.

Case 1.—A. B., aged twelve years, was admitted to the Babies Hospital, Jan. 31, 1935, because of periodic convulsions since the age of three years and failure of the right half of the face to grow normally. The history, obtained from an Italian father, was incomplete because of the language difficulty. The patient was an only child. Known members of her family were not afflicted either with similar disease or with heritable traits such as color-blindness, early graying of the hair, streaks of gray in the hair, birthmarks, hemophilia, or obesity. She was normal at birth; she walked, talked, and acquired control of the bladder and rectum at about two years. Previous illnesses included chickenpox at seven years, scarlet fever at eight years, and whooping cough at nine years; she was subject to frequent colds with tonsillitis.

The first convulsion occurred at the age of three years following an attack of vomiting. The left hand started to jerk first, then the left foot, then the right eye; the seizure lasted five hours. The second convulsion occurred a year later. The attack, similar to the previous one, included vomiting, headache, and involve-

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ment chiefly of the left arm, left leg, and right side of the face; to a lesser extent of the right arm and right leg. It lasted four hours. Gradually the attacks became more frequent. From the time she was five to the time she was ten years of age, they were mild and lasted only a few seconds. During the two months preceding admission they had become more severe, with as many as six attacks a day, lasting from thirty seconds to five minutes. They were always worse in the winter than in the summer. There was no relation to infection, fever, the time of day or night, excitement, or food. A premonitory aura was present in the form of faintness with buzzing in the ears for a few minutes before an attack. The patient saw a red, white, and blue butterfly. The bed seemed to go "upside down." Often her face turned red, she began to laugh and felt a tickling in her neck. She never fell and hurt herself but got to a chair or a bed before the convulsion started. The left hand began to feel stiff, and the patient felt the blood "going up and down her arm." Her right eye hurt and burned between the attacks, and her left

Fig. 1.—Case 1. Lesion on forehead and face showing typical "sclérodermie en coup de sabre."

eye itched. In an attack she turned blue, was "stiff at first, and then began to shake." The father described a carpopedal spasm. The patient said she remembered the jerkings but was unable to speak for from ten to twenty minutes even though she wanted to. There was no loss of sphincter control.

At six or seven years of age (three or four years after the onset of convulsions) the parents noticed a spot on the patient's forehead like a scratch, which bled easily. There was no history of trauma. This spot gradually increased in size, involving the entire right side of the nose and part of the scalp.

The patient's speech was pulpy and inarticulate. She had been in an ungraded class at school because of her convulsions, but she was said to have done well with lessons. She got on well with other children, and played fairly actively. She was left-handed naturally, but because of training in the use of the right hand had become ambidextrous.

Physical Examination.—The temperature was 99.6° F. The blood pressure was 120 systolic and 58 diastolic. The weight was 41 kg. The patient was a tall, well-nourished girl whose mental status was definitely below normal for her age, and some parts of the examination were rendered more difficult on this account, although the patient tried hard to cooperate.

The facial asymmetry which was due to atrophy of the right side of the face and forehead was striking. There was on the right side of the nose markedly sclerodermic tissue, which formed a groove as it reached the forehead and was most marked on the right side of the scalp, with some tenderness over this area. There was another streak of atrophic skin and subcutaneous tissue which started

Fig. 2.—Case 1. Alopecia of scalp continuous with "sclérodermie en coup de sabre."

just in front of the right ear, spread downward, and fanned out over the cheek and mandible. Tight adherence of the skin to the underlying structures and thinness over the affected areas were very noticeable. The skull beneath the area of scleroderma felt uneven, with a definite indentation about 2 by 2 cm. in size to the right of the midline. "Sclérodermie en coup de sabre" seemed to fit perfectly as a term to describe the lesion on the forehead and face (Fig. 1). There was alopecia of the scalp over the involved area (Fig. 2). The right eyebrow was much shorter than the left. A few brow hairs were seen to the right of the median line, and laterally came the gap. The eye sockets were on different levels, the nares were on different horizontal and frontal planes, and the right nostril was smaller than the left. The tip of the nose deviated to the right. There was hypoplasia of the mandible. Examination of the eyes revealed slight lateral

nystagmus with myopia; vision was more defective on the right than on the left. There was paralysis of the left superior rectus muscle, with overaction of the right inferior oblique. Some of the incisors and canines showed erosion of the enamel surfaces. Some molars were broken off at the gum margin; some were missing entirely. The gums were red, swollen, and tender. Numerous pigmented moles were scattered over the body, especially over the back.

First Neurological Consultation (Dr. Walter Klingman) (Examination made shortly after a convulsion).—There was some unsteadiness in walking, with tendency to veer to the left, especially in walking a line. There was considerable lordosis and scoliosis of the upper thoracic and lumbar spine, which seemed to be exaggerated in walking, giving almost a retropulsion attitude. The patient performed nonequilibratory tests more slowly with the left upper and lower extremities than with the right. The deep reflexes were hyperactive, more so in the lower than in the upper extremities. There was extension of the great toe on plantar stimulation, but it occurred frequently without stimulation, so that its value was doubtful. The abdominal reflexes were active and equal. There was asymmetry of both the hard and the soft palates because of atrophy of the right side, and atrophy of the right side of the tongue but with excellent preservation of muscular activity (Fig. 3). There was increased sensation to touch and pain over the area of scleroderma and alopecia. The rest of the examination of the cranial nerves was negative. On a subsequent occasion Dr. Klingman noted that the uncertainty in the gait, and the ataxia in the extremities on the left, was very much less than previously, and probably was due to temporary functional interference because of the convulsion.

Fig. 3.—Case 1. Atrophy of right side of tongue.

Skin Consultation.—Dr. Gross reported that the lesion on the forehead was a typical case of "sclérodermie en coup de sabre." Dr. Beatrice Kesten reported, "Without prolonged previous study one is not in a position to say whether this is the end stage of scleroderma or hemiatrophy. It may be that it merely represents the skin manifestation of the general atrophy which involves all the underlying tissues. The absence over the rest of the body of other sclerodermic patches weakens the diagnosis of scleroderma over the involved area."

Laboratory Findings.—Except for a trace of albumin, the urine was normal. A complete blood count yielded normal findings. The basal metabolic rate was 27 per cent below the normal average for girls of her age and size, according to the Boothby-Sandiford modification of the DuBois standards. Lumbar puncture

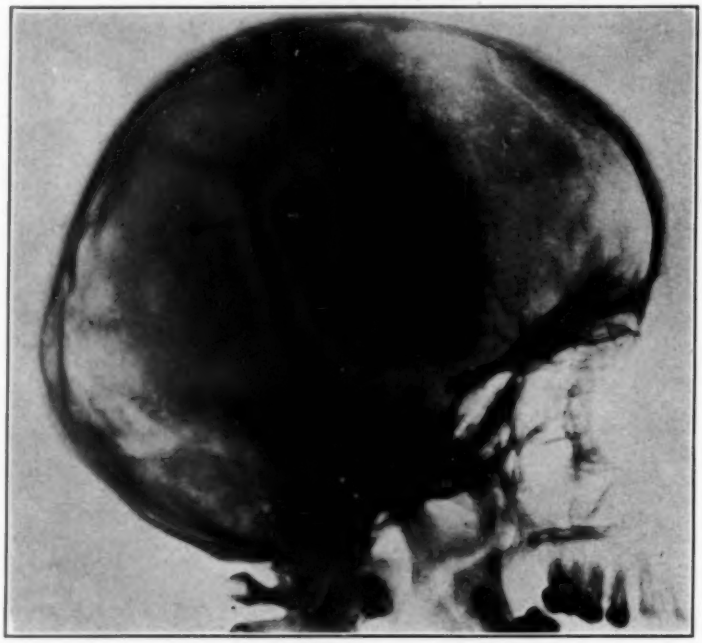

Fig. 4.—Case 1. Roentgenogram showing calcification in the posterior parietal region (full lateral plane projection).

gave clear spinal fluid under a pressure of 55 mm. of water. The chemistry of the spinal fluid showed sugar, 60 mg. per hundred cubic centimeters; chlorides, 719 mg. as NaCl; protein, 50 mg. The Kahn test on the blood was negative. The Mantoux test (0.1 mg. O. T. intradermally) was negative. Chemical examination of the blood serum showed per 100 c.c.: calcium, 10.6 mg.; inorganic phosphorus, 4.4 mg. Roentgenograms: Stereoscopic study of the skull was made in five positions. They showed asymmetry of the frontal sinuses with hypoplasia of the entire right frontal region, the right maxillary sinus smaller than the left, retardation of ethmoidal development, the nasal cavity smaller and the floor higher on the right, the dental process of the upper maxilla and the teeth undersized on the right, multiple areas of intracranial calcification in the right posterior parietal region in a zone 2 cm. lateral to the midline (Figs 4 and 5). Encephalography was un-

successful. The dental films showed hypoplasia of the incisal edges of the upper central incisors, the lower centrals and laterals, lack of development of the upper right second and third molars, the upper left second and third molars, and of the lower right third molar. The lower first molars on both sides were missing; pos-

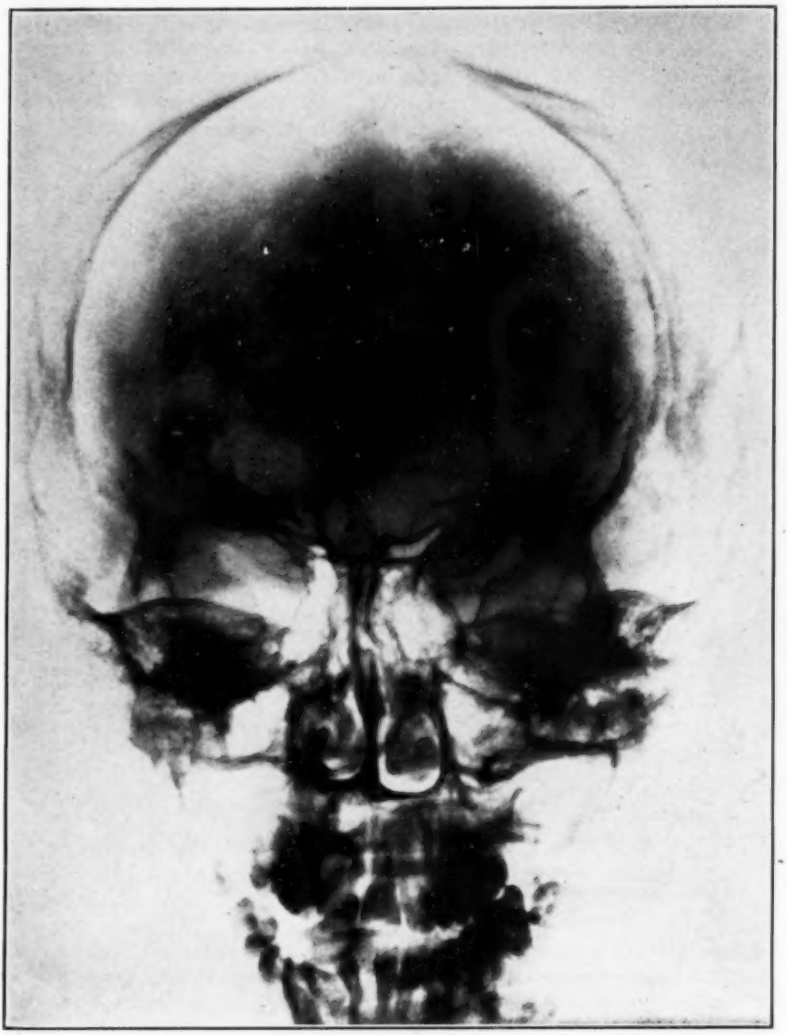

Fig. 5.—Case 1. Roentgenogram showing the same lesion as in Fig. 4 (full frontal plane projection).

sibly they had been extracted. The roots of the lower right second molar were considerably smaller than those of the lower left second molar.

The reaction of the sympathetic nervous system was tested to each of several drugs injected subcutaneously. Epinephrine, 0.5 c.c. of a 1:1000 solution, was

used to determine if there was an acceleration of the pulse of 30 beats or more; if the blood pressure rose 10 mm. or more; if there was an oculocardiac reflex; if there was a rise in respiratory rate or in body temperature; whether there were dermographia and facial pallor; whether there was a high grade tremor, a decrease or disappearance of eosinophiles, or glycosuria. Pilocarpine, 0.006 gm., was injected to determine whether the blood pressure fell 10 to 20 mm., if there was excessive lacrimation and salivation, whether there was a dermographia, whether there were gastrointestinal symptoms (epigastric pain, vomiting, tenesmus, or diarrhea), whether there were headache and vertigo, and if the eosinophiles increased relatively and absolutely. Physostigmine, 0.0015 gm., was given to determine if there was a

Fig. 6.—Case 2. View showing alopecia of scalp and lesion of right side of forehead and nose. Note deviation of nose to right and pulling of mouth to right and upward.

change in blood pressure, an increase in the respiratory rate; or if there were palpitations, abnormal pulsations, and an oculocardiac reflex; if there was increased lacrimation, salivation, or sweating; if there was dermographia, flushing, or facial pallor; if there were tremors or twitchings; if there was headache, drowsiness, or restlessness; if there was a change in the leucocytes, especially the eosinophiles; and if a glycosuria occurred. All responses to these drugs in our patient were considered to be within normal limits, and nothing was noted which showed a difference in the two sides.

Tactile sense over the distribution area of the right fifth cranial nerve was tested with von Frey hairs; the two sides of the face reacted in like fashion.

Measurements of surface temperature by means of thermocouples showed that there was practically no difference between the two sides. The ability to perceive heat seemed slightly increased over a small area in the right supraorbital region, within the area of scleroderma where the skin was exceedingly thin.

Course.—During her stay in the hospital (thirty-five days) the patient had frequent convulsions, numbering as many as eight in twenty-four hours and lasting from one to two minutes. Some of them were preceded by auras. They were clonic in type and involved both sides of the body in each attack observed, though the twitchings of the left side were generally noted to be more marked than on the right. There was no loss of sphincter control, but there was loss of consciousness. There was no carpopedal spasm at any time. The patient was quite exhausted after the attacks. During the intervals she was often moody and would not speak to anyone. At other times she was cheerful and talkative. She had periods of emotional instability and periods of giggling. Three days before discharge the patient had a very severe attack, which lasted for twenty-four hours, and in which she was disoriented and had marked convulsive movements. A ketogenic diet, tried for two weeks, had no beneficial effect on the convulsions.

Fig. 7.—Case 2. View showing atrophy of right cheek, and lesion of right side of forehead and nose.

The possibility of cosmetic improvement from plastic surgery was considered, but it was felt to be unwise before the patient had attained her full growth and before there was evidence that the lesion had stopped progressing.

The patient was referred to the Neurological Institute for deep-x-ray therapy of the cerebral calcification. She was seen for the last time in our clinic five weeks after her discharge. A social worker was unable to persuade the patient's mother to bring her back, when she was seen eleven months after her stay in the hospital.

CASE 2.—A. R., aged four years and ten and one-half months, was admitted to the Stanford Hospital on August 19, 1925, because of attacks of convulsions, accompanied by vomiting, in January, April, and August, 1925. The family history was negative. The patient was delivered by forceps after a second stage of labor which lasted four hours. The child's development was normal, though the dietary was poor. For the two years previous to admission he had a habit of biting

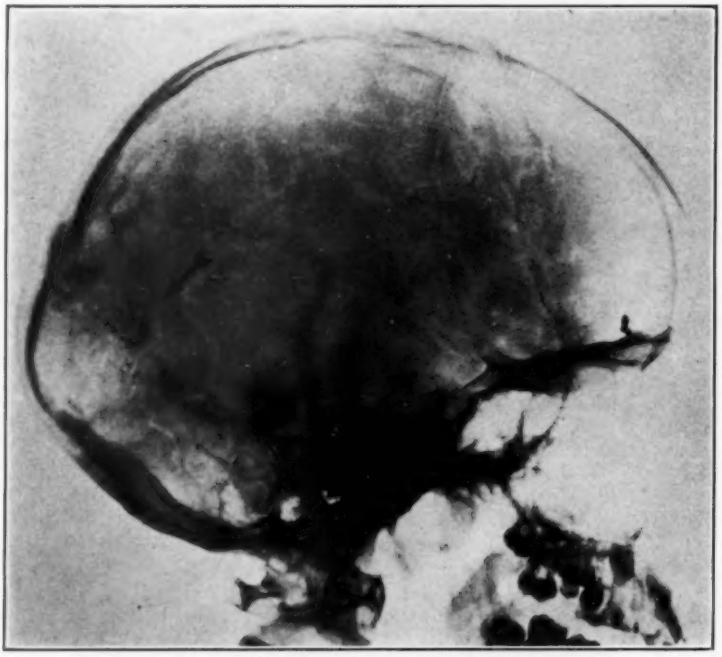

Fig. 8.—Case 2. Roentgenogram showing calcification in the occipital region. Note the parallel lines in the lesion. A small area of calcification may be seen in the region of the pineal gland (full lateral plane projection).

his nails. About February, 1924, the boy was struck on the head with a toy shovel; there was no loss of consciousness. About August, 1924, he was struck over the right eye by an arrow. The wound bled a little and later became infected; there was no loss of consciousness at the time of the accident. About January, 1925, after eating much fruit, the patient had abdominal pain followed by vomiting and a convulsion. He had pertussis in March. There were three subsequent convulsive attacks, one in April and two in August. In these attacks the head was drawn to the left, there was twitching of the face, jerking of the left arm and leg, and jerking of both sides. Vomiting continued throughout the attacks, which lasted from two to three hours.

Physical Examination.—First Admission (Aug. 19, 1925): The only abnormalities were a palpable spleen, an undescended right testis, and a depressed scar over the

right frontal region from above the hairline down to the inner end of the right eyebrow. The skin over this scar was somewhat discolored. The neurologic examination including the eyegrounds was negative. A roentgenogram of the skull was negative, as was also a Wassermann test on the blood.

Second Admission (July 17, 1931): The patient had only one convulsion (1926) since the previous admission. About August, 1926, his mother first noticed the

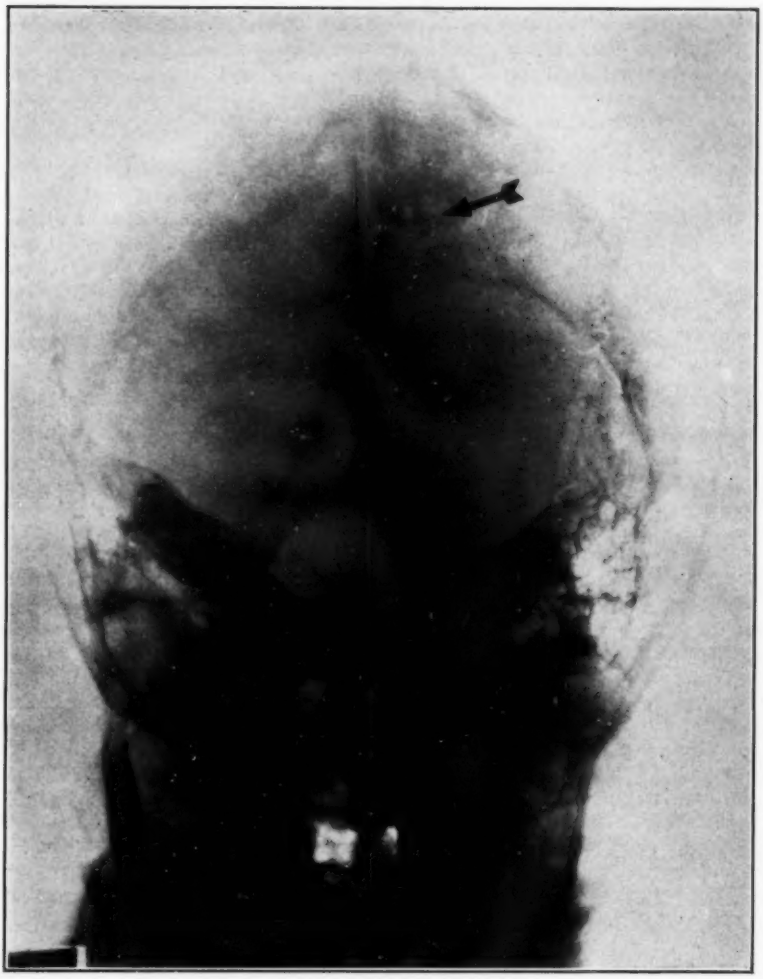

Fig. 9.—Case 2. Roentgenogram showing same lesion as in Fig. 8 (full frontal plane projection).

asymmetry of his face, the right side appearing smaller than the left. This had persisted and possibly increased. Physical examination at this admission showed that the right half of the face was much flatter than the left. There was a depression above the inner end of the right eyebrow beneath a large scar running vertically two or three fingerbreadths beyond the hairline. The subcutaneous fat

beneath the scar on the right cheek seemed atrophied so that the outlines of the zygoma and the maxilla could be easily palpated (Fig. 6). The right palpebral fissure was wider than the left; the lower lid was pulled downward, but there was no ectropion. The nose had a longitudinal furrow to the right of the midline, as though it was involved in the original injury. The right nostril was smaller than the left. The nose deviated to the right. The mouth was pulled to the right and upward (Fig. 7). The lips did not close completely, except by tensing the orbicularis oris. The raphe of the palate was in the midline. The right ramus of the mandible looked smaller than the left from the outside, but the lower teeth on both sides were set in symmetrical curves. Roentgenogram: the skull appeared symmetrical, as did the facial bones. Definite, abnormal calcification was present. This calcification was situated just to the right of the midline, in the occipital region (Figs. 8 and 9). It was not present at the last examination.

Third Admission (Feb. 3, 1933): About Dec. 20, 1932, the patient had a brief upper respiratory infection, at which time he was markedly somnolent and difficult to rouse. Three or four days after the onset he was found in a state of unconsciousness, but he was not incontinent nor did he bite his tongue. The attack was brief without ensuing drowsiness or headache. He complained of feeling dizzy. Since then, he had frequent brief attacks of semiconsciousness (petit mal?). He also had had generalized convulsions about once a month for the last eight months. Physical examination showed that the atrophy of the right side of his face was more marked than before. Neurologic examination showed the left knee jerk was more active than the right, and there were positive pyramidal tract signs on the right, as revealed by the Gordon, Oppenheim, and Babinski tests. The examination of the cranial nerves was negative. The apparent deviation of the tongue to the right was due to atrophy. There were no sensory or coordinative disturbances. The Mantoux test with 0.05 mg. old tuberculin was negative. Roentgenogram: The appearance of the cranial bones remained normal. The calcification reported at the last examination was still present and appeared to have increased somewhat. The pineal was definitely calcified, and was either displaced forward or perhaps was at the anterior limit of normal. February 9, 1933: The patient had a generalized convulsion. On Feb. 11, 1933, after receiving pilocarpine, sweating was greater on the right than on the left side of the face. The application of ice to the back of the neck gave a definite and marked pilomotor response from the right clavicle to the nipple and in the right axilla; the reaction was very slight on the left. Both tests were interpreted as indicating hyperactivity of the sympathetic system on the right side. The parents refused operative interference, and the patient was given sedatives and a ketogenic diet.

Fourth Admission (Jan. 10, 1934): The patient had frequent generalized convulsions since the last admission. One observed on the night of admission involved the left side of the face, neck, and the left arm. The eyes turned to the right. Neurologic examination showed nothing new. Encephalogram: No additional information was obtained.

Course.—(Sept. 3, 1935). The atrophy was still more marked. The patient continued to have convulsive seizures, but they were not so frequent or so severe as before.

DISCUSSION

Archambault and Fromm's[1] contention that progressive facial hemiatrophy is a well-defined symptom-complex is amply substantiated. They pointed out that the various lesions which have been described involve the sympathetic division of the vegetative nervous system at some point in either its central or its peripheral course. They em-

phasized the fact that the etiology of this condition still remains obscure but feel that frequently antecedent infections or trauma to the face or neck may be the inciting factor.

They also stated that the atrophic process may involve all the structures of the face; the skin, the subcutaneous fat, the connective tissue, and the muscles and bones. Wartenberg[2] emphasized the fact that the skin may escape entirely, or that the subcutaneous fat and the connective tissue may be greatly affected before or without concomitant involvement of the skin; also Cassirer[3] and others said that bone involvement is inversely proportional to the age period at which the hemiatrophy has its onset.

The connection between progressive facial hemiatrophy and scleroderma has been discussed a great deal in the literature, and is far from solution. Several authors as early as 1870 suggested that scleroderma was the etiologic factor in facial hemiatrophy. Archambault and Fromm[1] considered Cassirer[3] to be the most active supporter of this theory, although he claimed that facial hemiatrophy may be only a special form of scleroderma. In both conditions there is a disappearance of subcutaneous fat and an atrophy of the skin, with adhesions to the underlying structures, especially to the bone. They also pointed out that, although the skin as a rule is involved, there are many instances when it escapes entirely. This was also true in the cases reported since Archambault and Fromm's monograph.[1] The unanswered question as to the relationship between facial hemiatrophy and scleroderma seems best summed up in their statement, "It is therefore evident that in certain instances the differentiation between the two may be absolutely impossible, but we do not think that, relatively common as it is, the association of scleroderma and facial hemiatrophy is adequate proof of their identity."

Archambault and Fromm[1] concluded from their review of the published cases that the occurrence of pigmentary anomalies is not uncommon. Since the publication of their article, Bernstein[4] has reported the case of a girl who had areas of pigmentation on the right side of the neck, in association with her facial hemiatrophy. Bruckner and Obständer's[5] patient had considerable pigmentation over the entire body. Of Chasanow's[6] eleven cases, seven showed pigmentary anomalies. Truffi's[7] case had pigmentation in association with atrophy of the left forehead, nostril, and temporal region. Pick's[8] patient showed pigmentation on the forehead, and that of Faber[9, 10] had so much pigmentation over her body that "she looked like a zebra." Gianneschi[11] described a brown pigmented area which extended from the forehead to the cheek bone in a woman sixty years of age. Lazarescu and Lazarescu's[12] patient showed pigmentation of the skin over the face.

The association of epilepsy with progressive facial hemiatrophy has been noted by other observers, and is discussed in the following extract from Archambault and Fromm: "The occurrence of epilepsy, whether of the so-called idiopathic and generalized forms, or of the jacksonian type, is . . . interesting. Wartenberg,[2] whose patient exhibited both, although the seizures were predominantly jacksonian, unequivocally expressed the opinion that there is more than pure coincidence between the two and erected a most elaborate hypothesis to affirm his position. We regret that we cannot here furnish the full detail of his theory, but the essential feature is that facial hemiatrophy, the primary clinical manifestation, would result from a lesion of the higher vegetative centers in the diencephalic floor, that disturbances of sympathetic innervation would soon affect the vasculature of the homologous cerebral hemisphere and thus predispose this hemisphere to subsequent toxic or infectious invasions, which would account for the occurrence of jacksonian seizures in the contralateral extremities. Up to 1925, Wartenberg had collected only four cases (including his own) of jacksonian epilepsy. Since that date we have found three additional cases, those of Lauber, H. G. Wolff, and our Case 2, all of them exhibiting generalized seizures. This brings the total number up to eleven, and we have no doubt that Wartenberg, like ourselves, has overlooked some cases. Nevertheless, we think that there is nothing astonishing in the fact that, rare as it is, facial hemiatrophy should occasionally appear in a person suffering from so common a disease as epilepsy. The number of such cases, even admitting that our count falls short, is still too insignificant when one remembers that the total number of cases of facial hemiatrophy thus far recorded probably exceeds 400. Again, it is well to bear in mind that not all cases of so-called jacksonian epilepsy indicate a focal cerebral lesion. The most alluring fact in connection with this problem is that in the majority of the eleven cases referred to, the convulsive episodes appeared some time after the hemiatrophy had become definitely recognizable. In this respect, the literature would substantiate Wartenberg's views."

In an attempt to evaluate Archambault and Fromm's[1] contention that eleven instances of epilepsy in 400 cases of facial hemiatrophy is not an incidence worthy of note, we determined that there were approximately eighteen cases of epilepsy (listed as grand or petit mal, or a combination of both) diagnosed in the pediatric department of the Vanderbilt Clinic in the year 1934, and that in the same year the total number of new patients admitted to the clinic was 2,259. In one instance, the incidence is approximately 3 per cent, and in the other it is 0.8 per cent. Although this is a rough estimate, it seems as though the percentage in the cases collected by Archambault and Fromm is more striking than they concede, especially since they state that "the

most alluring fact in connection with this problem is that in the majority of the eleven cases referred to, the convulsive episodes appeared some time after the hemiatrophy had become definitely recognizable."

It is pertinent to point out that in our first case, the facial hemiatrophy did not appear until the third or fourth year after the onset of convulsions. It seems fair to conclude that the convulsions in this patient are directly related to the cerebral calcification. In the second case, the sequence of events suggests that the convulsions were related to a cerebral lesion which later became calcified. The relation of the calcification to the hemiatrophy in both cases is not clear.

Archambault and Fromm did not mention cerebral calcification in any of the cases which they reviewed, nor have we found any record of this lesion in association with progressive facial hemiatrophy in publications since their article. Since the technic of demonstrating such cerebral lesions is of comparatively recent origin, it is possible that they have been present and that either roentgenograms were not made or the technic used failed to demonstrate them.

Camp[13] has given the following classification of cerebral calcification:

I. Physiologic calcification.
   1. Pineal gland.
   2. Choroid plexus.
   3. Falx cerebri.
   4. Tentorium.
   5. Meninges.
   6. Pacchionian bodies.

II. Pathologic calcification.
   1. Neoplastic group (gliomas, endotheliomas, suprasellar cysts, cholesteatomas)
   2. Nonneoplastic group.
      (a) Vascular: 1. Aneurysms.
                    2. Angiomatous malformations.
                    3. Hematomas.
      (b) Old abscesses.
      (c) Tuberculoma.
      (d) Parasitic cysts.
      (e) Encephalitic lesions.

In a series of 781 verified lesions of the brain observed at the Mayo Clinic in the ten years previous to the publication of his article, calcification in the lesion was found by x-ray in 7.6 per cent of the cases.

From the evidence at hand, it does not seem possible to classify definitely the type of calcification which our patients showed. Owing to the position, size, and type of the lesion, it is possible to rule out

calcification in the pineal gland in the first case. At the third admission of the second patient, the pineal gland was calcified but could be differentiated from the pathologic calcification. The lesion did not suggest calcification of the choroid plexus, tentorium, or falx in either case. Meningeal calcification is rare according to Camp,[13] who saw only one case. Pacchionian bodies show very minute areas of calcification. As evidence against the various pathologic types of calcification, the character of the roentgenographic lesion in our cases does not conform to the well-recognized types seen in various neoplasms. Our first patient had no neurologic signs which suggested a tumor, except the presence of convulsions. On the third admission, the second patient had a more active knee jerk on the left than on the right and positive pyramidal tract signs on the right. However, a year later these signs had not increased, and as two years later the convulsive seizures were not so frequent or so severe as before, it seems fair to conclude that the calcification did not represent a neoplasm.

There was nothing in the history, physical examination, or laboratory findings to suggest an old abscess or a parasitic cyst in either case. The negative Mantoux tests in both of our patients argue against tuberculoma. Camp[13] stated that Ström mentioned the presence of calcification in chronic encephalitis, but said he had not been able to find any proved case in which calcification was demonstrable in the roentgenogram in any of these conditions. Dyke[14] concurs in this opinion. This leaves us the vascular lesions to consider. A calcified cerebral aneurysm usually involves the circle of Willis, whereas our patients' lesions are not in the right position to enable us to make this diagnosis; also, their ages argue very much against it. Calcified hematomas very frequently follow trauma, which was lacking in the history of the first case. It was present in the history of the second case, however, but calcification in hematomas that have been observed roentgenographically give an irregular, dense shadow, somewhat triangular in shape, unlike those seen in either roentgenogram.

The lesions in our patients conform most closely to calcified hemangioma. Greenwald and Koota[15] have recently reviewed the literature on the syndrome of associated facial and intracranial hemangiomas, which is sometimes known as Parkes Weber-Dimitri's disease. These authors found calcification in cerebral hemangiomas to have been reported in sixteen out of the fifty-eight unconfirmed cases, and in only one of the twenty-four confirmed cases. The typical lesion as described by Parkes Weber[16] and Krabbe[17] shows a large mass of calcified racemose vessels, usually in the occipital area. The lesions in our patients are not as large as in many of the reported cases, but they do conform with them in position and character. In the second case, two parallel lines of calcification are plainly visible in part of the lesion, suggesting a tubular structure.

Two familial types of calcification have been reported. Geyelin and Penfield[18] have reported an unusual family, in which the father and all four children had epilepsy. Roentgenograms of the skulls in four of the cases showed discrete patches of calcification. From microscopic study of a specimen obtained at operation, glial changes were found about the smallest blood vessels. This process resulted from what they called an "endarteritis obliterans" or "endarteritis calcificans." Our patients had no family history of convulsions to suggest the clinical entity described by Geyelin and Penfield. Fritsche[19] reported another familial type of cerebral calcification. Three siblings, whose parents were second cousins, all had varying degrees of mental backwardness, and two had difficulties in either gait or speech. Roentgenograms of all three showed calcification in the basal ganglia and in the white matter of the hemispheres. There was no operative or pathologic report.

SUMMARY

1. Two cases of progressive facial hemiatrophy with cerebral calcification and convulsions in a girl twelve and a boy fifteen years old are presented.

2. Roentgenograms demonstrating cerebral calcification conform most closely to proved cases of calcified hemiangioma.

3. It is believed that in the first case the convulsions, which antedated the hemiatrophy by three or four years, were directly related to the calcified cerebral lesion. In the second case, also, it is believed that the convulsions were related to a hemangioma, which later became calcified. It does not seem probable that the history of trauma bore any relation to the convulsions.

4. The relation of the intracranial process to the hemiatrophy in both cases is not determined.

Abstracts of cases of progressive facial hemiatrophy reported since 1930 are given:

In 1930 Bernstein[4] reported the case of a twenty-year-old girl with right-sided atrophy of the face, tongue, and the sternocleidomastoid muscle, whose symptoms appeared at eight years of age. No etiologic factor was apparent. There was an accompanying atrophy of the left lower extremity, and an impression of scleroderma was obtained here owing to lack of subcutaneous fat. There was also atrophy of the bones of the left lower leg. Alopecia was present on the right side of the head and areas of pigmentation on the right side of the neck.

In the same year Surat[20] described two cases: the first, a sixty-year-old woman who had had sharp pains over the right side of her face at the onset of her illness, fifteen years before. No etiologic factor could be determined. The roentgenogram showed atrophy of the right mandible and maxilla. The second case was that of a thirty-eight-year-old woman who gave a history of "trigeminal neuralgia" on the left side of the face for seven years. The face appeared asymmetrical, being thinner on this side, and the left eye socket was deeper. There was no bone atrophy.

Eitner[21] in 1931 described a case of right facial hemiatrophy in a young woman in whom the etiologic factor was considered to have been the introduction of a caustic needle into a hemangioma of the face at the age of four years.

Rocher's[22] patient (1931) was a female infant five months old, who had atrophy of the lobe of the right ear, associated with facial hemiatrophy, hypoplasia of the inferior maxilla, and paralysis of the facial nerve. Rocher believed that this pathology had a congenital basis.

In the same year, Wagenhals[23] reported the case of a girl, eleven years old, the onset of whose facial hemiatrophy occurred at eighteen months of age, when a pale streak was first noted on the face to the left of the nose; the upper lip was also involved. A few months later, the left side of the face began to appear smaller. No definite etiologic factor was apparent. Roentgenograms showed a slight difference in size between the malar bones and zygomatic arches on the two sides.

Mollaret[24] (1932) stressed the association of facial hemiatrophy with syringomyelia, scleroderma, and the lipodystrophies. His patient, a girl of twenty-five, had a negative history except that she had had migraine. Three years previously the atrophy appeared on the left side of the face. She had a narrowed palpebral fissure, enophthalmos, and miosis on the left. Four years after the onset, following an alveolar abscess on the left side, there was an apparent retrogression of the process over a period of two years.

Bruckner and Obständer's[5] patient (1932) was a woman aged sixty-one years, in whom no etiologic factor could be demonstrated for a facial hemiatrophy. At fifty-eight years of age, she had had sharp pains of the right side of the face and about the eye, with lacrimation. There was considerable pigmentation over the entire body.

Chasanow[6] (1932) described twelve cases. The fact that encephalitis had occurred in five of the twelve patients is striking. From some of the descriptions, one might be inclined to think that a Parkinson syndrome following the encephalitis could account for the appearance of the face, rather than to explain it on the basis of a facial hemiatrophy.

In 1932 Yater and Cavanaugh[25] described the case of a girl aged seventeen years who complained that three years before there had appeared a depression on the right side of her forehead and that the skin on the right side of her face had become yellowish brown. There was discoloration on the right side of the neck. No etiologic factor was noted.

Marinesco, Kreindler, and Façon's[26] patient (1932) was a woman twenty-three years old with left facial hemiatrophy which, commencing in infancy, progressed up to the age of twelve years and then remained stationary. The left side of the face was covered with a vascular nevus which spread down the neck. There were pigmented and vascular nevi on the right side of the body and on the right side of the chin. Atrophy of the bones of the left side of the face was present. They felt that this was a case of "alternating" hemiatrophy. Tests with adrenalin, pilocarpine and other drugs gave differences on the two sides, which the authors believed were evidence of a left-sided sympathetic disturbance.

In 1932 Flint[27] emphasized the frequency with which these cases are associated with epilepsy or some psychic abnormality. His patient, a girl aged twenty-four years, was peculiar and moody. Her mother had attacks of petit mal, and her sister was subject to melancholia. At twelve years of age, this patient had had a right-sided facial paralysis which lasted a month. At fifteen, a vertical groove ("coup de sabre") appeared on the forehead. At seventeen, there were corneal ulcers; at twenty-three, the right pupil was larger than the left and did not

react to light. There was right enophthalmos. Flint believed that facial hemiatrophy is preceded both by trigeminal disturbances and by injury to the sympathetic nervous system.

Sorsby and Shaw[28] (1932) reported the refraction findings in nine cases of congenital torticollis associated with hemiatrophy of the face. Not only was the affected side of the face grossly smaller, but the diameters of the affected orbit were also smaller. In only one case was there a marked difference in the refraction of the two eyes, so that the authors stated it was justifiable to conclude that influences in the development of the orbit do not affect the state of refraction in the eye.

Léchelle, Thévenard, and Joseph[29] (1933) described a woman aged thirty-five years, the onset of whose disease was at twenty-eight with paralysis of the right side of the face, attributed to chilling and accompanied by pain. The paralysis cleared up in three months. Some time afterward, atrophy was noted on the same side. At thirty-one years of age the patient complained of pain in the upper and lower teeth on the left side and had a feeling that her teeth were "too large." There was adiposity from the waist to the knees. A roentgenogram showed osteoporosis of the facial and maxillary bones. The syndrome developed progressively and slowly over a period of ten years.

Stief[30] in 1933 reported the case of a woman sixty-four years old. At sixty-three years of age she noted that the right side of her face was thinner than the left; the asymmetry increased rapidly during the following year. Keratitis and cataract developed in the right eye, and alopecia on the right, most marked over the occiput. There was also some atrophy of the right side of the tongue. Besides this, there was slight atrophy of the right side of the face. The right lower leg was atrophic. There was scleroderma over the middle third of the right lower leg. The left lower leg showed moderate scleroderma. At autopsy it was found that the whole right side of the body was atrophic, including the kidney, ovary, adrenal, and vocal cords. The chief lesion of the right side of the brain was vascular stasis and dilatation; on the left the tissue was anemic and showed a marked degree of necrosis. The right cervical sympathetic ganglion showed an infiltration of round cells and degeneration of nerve cells and fibrils. Like Archambault and Fromm, Stief favored the theory of a sympathetic lesion as the cause of the facial hemiatrophy.

Bøe[31, 32] in two articles (1933 and 1934) described a woman thirty-eight years of age. Following an attack of measles at the age of eight years, she developed progressive atrophy of the left half of the face, tongue, and palate, without scleroderma. There was definite atrophy of the skin and also of the masseter, temporal, and buccal muscles. The tongue deviated to the left. A roentgenogram showed some atrophy of the upper maxilla, left frontal bone, zygomatic arch, and left inferior turbinate bone. An expansion prosthesis of the mouth was performed on this patient.

Truffi's[7] case (1933) was that of a woman aged twenty-four years who had had hemiatrophy since the age of eighteen years. The etiology was unknown. There was atrophy of the left forehead, nostril, and temporal region, with pigmentation, also scleroderma under the eyelid and in the sternoclavicular region. A roentgenogram showed larger frontal, maxillary, and ethmoid sinuses on the left than on the right, the median septum of the sphenoidal sinus displaced to the left, the left mastoid area larger and more pneumatized than the right and the left side of the hard palate lower than on the right. Roentgen ray therapy was given over the left cervical area. The scleroderma was greatly helped, as was also the atrophic lesion over the left temple.

Pick[8] (1933) described a man forty-four years old, the onset of whose hemiatrophy had occurred twenty-nine years previously. He developed a lesion over

the left side of the forehead which was diagnosed as scleroderma. On physical examination he showed asymmetry of the face, with the tip of the nose deviated to the left. The left nostril was small, with a depression over the maxilla. On the forehead there was a typical "coup de sabre" lesion projecting into the scalp, with alopecia over this area. The skin of the forehead was pigmented and atrophic. A groove, which apparently extended down to the bone, could be felt. A roentgenogram showed osteoporosis of the lateral part of the skull and of the left maxilla. Histologic study of the skin showed sclerosis with atrophy and slight hyperkeratosis. Pick felt that this lesion was scleroderma, rather than a facial hemiatrophy, although the picture accompanying his article shows a lesion identical with many cases which have been reported as typical cases of hemiatrophy, and very similar to our cases.

Worms[33] (1933) reported two instances of what he considered to be aborted cases of facial hemiatrophy. A twenty-one-year-old man had an operation for right-sided mastoiditis. Several weeks after the operation he began to experience curious sensations on the right side of his face, and three months later he noticed that his face was smaller on that side. Sweating and vasomotor differences were striking on the right side; also there was hyperesthesia. The occulocardiac reflex on the right gave no reaction. There was right enophthalmos. Two small areas of alopecia, from 3 to 4 cm. in diameter, occurred in the right temporal region and, near them, patches of very thin hair. The second case was that of a sixty-year-old woman, the onset of whose illness began with sensations of heat and pain in the right cheek. Several teeth were extracted from the lower jaw. Three years later she had pain in the right side of the face. This pain was followed five or six months later by diminution in size on that side.

In 1934 Stiefler[34] described a fourteen-year-old boy who had been knocked unconscious by a fall from a window at the age of two years. However, no permanent injury was apparent at the time. At six years of age the left side of his face became smaller; at ten a groove developed above the right eye, with alopecia. At twelve, there was alopecia on the left side. At thirteen, he started to have attacks of unconsciousness but without convulsions. A roentgenogram showed slight asymmetry of the skull. The occipital and temporal areas were flattened on the right. The bones of the face were smaller on the left than on the right.

Recht[35] in the same year described two patients, one a woman thirty-seven years old, whose onset was at the age of twenty-six, with headache. She was treated for syphilis from the time she was thirty to the time she was thirty-four years old. At thirty-seven years of age she noticed that the right side of her face was beginning to sink in, that she had alopecia over the temples and occiput, and that she had no eyebrows or eyelashes. The second patient was a thirty-two-year-old woman, who had had grippe (? encephalitis) at eighteen years of age; subsequently she had psychic disturbances, and the right side of the face became smaller.

Also in the same year Euzière, Vidal and Mas[36] reported a case in a man forty-two years of age who had had progressive flattening of the right cheek for the previous nine years. Several years after onset, progressive atrophy of the tongue on the right side was noted. Horner's syndrome was present on the right. A roentgenogram showed atrophy of the posterior wall of the sella turcica.

Faber[9, 10] described a woman fifty-five years old, the left side of whose face was somewhat smaller than the right, especially over the chin. The skin was wrinkled, atrophic, and discolored by black pigmented granules. The atrophy affected skin, adipose tissue, and the mucous membrane of the left lower lip. She had so much pigmentation over her body that "she looked like a zebra." She was given thyroid for a supposed myxedema. The Wassermann test was markedly positive.

Bakács[37] (1934) reported a typical case of left facial hemiatrophy in an eight-year-old girl. There was no known etiologic factor. The skin, subcutaneous tissues and facial muscles of the left side of the face were markedly involved. After the disease appeared to be stationary (five years after onset) Bakács transplanted fat from the gluteal region to the face and obtained a satisfactory result. He observed the child for three years following operation.

Gianneschi[11] (1934) described a woman sixty years of age, who at four years of age had struck the left side of her forehead against a table. Infection set in, and later, brown pigmentation appeared in the scar tissue of the wound over the left zygomatic region. Eventually the left half of the face became thinner. The atrophy was progressive until the patient's twentieth year. Gianneschi described a diffuse telangiectasis and a brown pigmented area which extended from the forehead to the cheek bone. The skin was adherent to the bone and very thin. Another patch covered the middle part of the lower jaw on the same side. The left side of the nose and the left eye were affected. There was no involvement of the scalp or hair. Gianneschi did not feel that the original trauma was necessarily the etiologic factor responsible for the hemiatrophy.

Vinař[38] (1934) described a man, twenty-three years old, who had had an injury to the right temporo-parieto-occipital region with subsequent right facial hemiatrophy. A roentgenogram showed atrophy of the underlying bones. Horner's syndrome and Argyll Robertson pupil were said to be present on the right side. There was hyperesthesia over the distribution areas of the first and second branches of the right trigeminal nerve, and pharmacologic tests proved that there was a lesion of the sympathetic system on that side.

Lazarescu and Lazarescu's[12] (1934) patient was a man of seventy-six years, whose right facial hemiatrophy began in infancy but became more severe following trauma to the right side of his face. For one year before observation, his right eye had become red, there was increased lacrimation, and his sight was impaired. On examination he showed enophthalmos of the right eye, diminution of the orbital tissue, and ptosis of the right eyelid. There was asymmetry of the face with loss of subcutaneous fat and atrophy of the facial muscles, except the masseter, on the right side. The skin of the face showed pigmentation. There was a deep depression in the middle of his forehead. The patient had phases of depression, poor memory, inattention, and language difficulty.

Jonesco-Sisesti[39] (1934) reported four cases in which he felt that the hemiatrophy was due to a lesion of the trigeminal nerve. In the first case the left facial hemiatrophy was so marked that it dominated the clinical picture. The left malar and orbital bones were less developed than the right. There was a complete anesthesia of the left side of the face, a Horner's syndrome and paralyses of other cranial nerves. The second patient had a process similar to the one just described, but not so marked. The third case was similar to the other two, but paralyses referable to the trigeminal nerve were milder. The fourth patient was of interest, in that he had a left facial hemiatrophy, even though the bulbar lesion manifested itself clinically on both sides. However, the lesion was more marked on the left, where there was a Horner's syndrome and vasomotor and secretory disturbances. Jonesco-Sisesti described a fifth patient whom he first saw at the age of nineteen years. At three or four years, this patient had had a meningitis of unknown etiology. Following this he had abnormal lacrimation on the left and difficulty in closing the eye completely. A little while afterward the patient developed left facial hemiatrophy involving all the muscles, and roentgenograms showed atrophy of the skull on this side. The author felt the lesion was in the motor nuclei of the facial muscles.

Shumway[40] (1935) reported the case of a young woman with postneuritic optic atrophy, partial hemiatrophy and enophthalmos of one side of the face, loss of smell,

and partial loss of taste associated with recurrent attacks of facial palsy, some of which were preceded by pain. The diagnosis offered was polyneuritis of the cranial nerves, probably due to dental infection. Shumway doubted if the condition which the patient showed was a true hemiatrophy, though "facial hemiatrophy" is included with optic neuritis and facial paralysis in the title of his article. He thought that the hemiatrophy in his case was probably due to an inflammation of the fifth nerve.

Rakonitz's[41] (1935) case was that of a twenty-three-year-old male, whose onset was at nine years, with atrophy and shininess of the skin on the left side of the face and alopecia of the scalp. A roentgenogram showed osteoporosis of the left side of the skull. Over a period of two years the right side became slightly involved also. Rakonitz considered that a trophic and secretory involvement of the sympathetic nervous system was proved in this syndrome since by using an iodide and starch test he demonstrated in his case that the atrophy was limited to areas where the sweat glands were controlled by the sympathetic system.

Urechia and Retezeanu[42] (1936) described a woman thirty years old, the onset of whose malady began at eight years of age, when she was severely chilled. Following this a progressive muscular weakness developed in her left upper arm. At twenty years of age, she noticed an atrophy of the right side of her face. A roentgenogram of the skull showed no abnormality of the bones. The authors felt that the chilling which may have been a factor in the hemiatrophy did not explain the atrophy of the arm, which they classified as an Aran-Duchenne type. A healed pulmonary tuberculosis may have been a factor in the origin of the hemiatrophy. The authors conclude that the etiology of both conditions was not proved, and that their association was a coincidence.

Meyer[43] (1936) described three cases of facial hemiatrophy. The first was that of an eighteen-year-old girl, whose illness dated from an attack of scarlet fever in 1922, after which there was a right-sided alopecia. There was delayed dentition on the right side and imperfectly formed teeth. In 1924 a right-sided facial atrophy was noted, and a roentgenogram showed bone atrophy. The second was a thirty-year-old patient whose history revealed a disease (? encephalitis) occurring at seven years of age, which caused paralysis of some of the muscles of the left eye, and which was accompanied by fever. Some time after recovery, a discoloration of the skin over the right forehead was noticed, and later on a depression of that area, accompanied by an alopecia. This process became stationary at eighteen years of age. A left exophthalmos developed and sweating was more prominent on the left side. The third case report was that of a forty-three-year-old man who had developed left-sided atrophy about nine years previously. Perspiration on the left side was more marked than on the right. Meyer discussed different theories about facial hemiatrophy and its possible connection to other trophoneurotic disturbances.

Burket's report[44] (1936) dealt with a full-term spontaneously delivered male infant who showed true congenital bony ankylosis in the region of the left temperomandibular joint and alveolar ridges associated with maxillary and mandibular hemiatrophy. A left facial hemiatrophy and Horner's syndrome were present.

Three articles in Russian publications,[45-47] one in a Hungarian journal,[48] and one in a Brazilian publication[49] are not available at the New York Academy of Medicine.

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A NEW DOUBLE TELESCOPING CANNULA FOR CONTINUOUS INTRAVENOUS THERAPY

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CONTINUOUS intravenous therapy in pediatrics is now widely appreciated. Some who have tried to use this procedure have given it up because of technical difficulties. The greatest handicap has been clogging of the cannula by blood clot. In our own experience of seven years a block in the cannula has in one-third of the cases necessitated exposing a second vein, and on rare occasion when the venoclysis had to be continued, even a third vein was resorted to. In the remaining two-thirds of the cases, if a clot formed, the cannula was reopened by suction applied with a 10 or 20 c.c. syringe or by probing the cannula with a stylet. On few occasions the clot has been washed through into the vein by the injection of physiologic saline solution. This procedure, though effectual and usually uneventful, should be avoided for an obvious reason, the possibility of an embolism and pulmonary infarction.

For the past year we have been using a double or telescoping cannula, which I designed and which has been generally satisfactory. It consists of a cannula within another cannula, both being made to fit the same adapter. Should a clot obstruct the flow of solution through the inner cannula, it may be removed and cleaned while the flow of solution is maintained through the outer cannula. The inner needle or cannula may be cleaned, resterilized, and reinserted into the outer cannula as often as necessary, thus making it possible to have a continuously patent channel indefinitely except in the relatively rare instance when the clot extends into the vein itself and the flow becomes hindered beyond the cannula. In that case another vein would have to be resorted to if the injection were to be continued.

There are other advantages of this type of cannula. The small gauge of the inner needle (21) is beneficial, first because the pressure exerted by the column of fluid (3 to 4 feet) becomes greater, thus making a back flow of blood into the cannula less likely and, therefore, lessening the chances of clot formation. Second, in the event that after the surgical exposure of a vein it is found to be too small for the 18-gauge cannula, the inner cannula may be substituted instead of having to expose another vein. One is commonly confronted with this problem. The fine caliber of the inner cannula is, therefore, a definite aid. A third advantage of this cannula is that the rate of flow can be varied by using either the inner or outer cannula as is indicated for the particular

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case. This is especially helpful if saline solution or blood is given at a very slow rate. Fourth, in the case of transfusions through the single cannulas, it was necessary to change the cannula because blood seemed to hasten the tendency for clotting occasionally within it. The double cannula is, therefore, helpful in that one or the other may be used for transfusion. Thus, if the transfusion is given through the inner cannula, it can be removed and cleaned; if the transfusion is given through the larger outer cannula, it should be washed with physiologic salt solution before inserting the inner cannula.

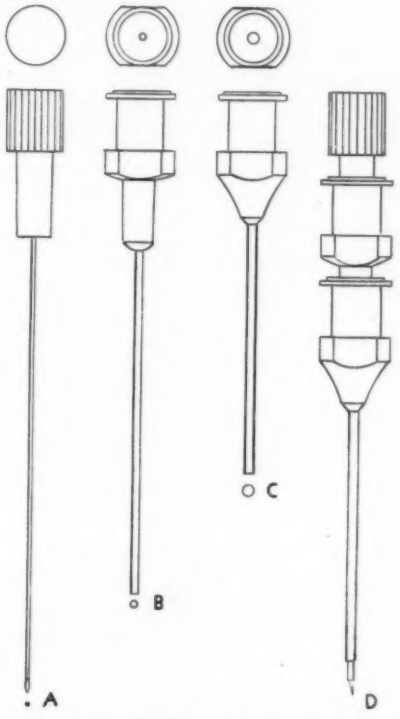

Fig. 1.—*A*, stylet; *B*, inner cannula, 21 gauge; *C*, outer cannula, 18 gauge; *D*, assembled double cannula.

We believe that the advantages offered by the double or telescoping cannula over the customary single ones in general use are adequate to justify its being tried.

1097 Park Avenue

The cannula described was made up according to my specification by Becton, Dickinson & Co., of Rutherford, N. J.

Since doing this work, it has come to my attention that a cannula similar to the one here described has been in use at the Jefferson Hospital of Philadelphia and is known as the Trumper telescopic needle. The Trumper telescopic needle is manufactured by George P. Pilling & Son Co.

Critical Review

GROWTH AND DEVELOPMENT

The Endocrine Glands and Growth (Continued)

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The Adrenal Glands

IN THE previous reviews of this series the activities of the pituitary and the thyroid glands in growth processes have been considered. It was pointed out that the pituitary gland, in some way, probably through hormones, exerts a controlling influence over many other endocrine structures in addition to secreting its own specific growth hormone. The thyroid gland, although under definite pituitary control, produces striking effects on the quality and rate of growth, through its secretion, thyroxin. Although the adrenals also are, to some extent, dominated by the hypophysis, their rôle in growth is more complicated and less generalized than is that of the thyroid. They are necessary for growth, primarily because life itself depends upon adequate production of the adrenal hormone, cortin. In addition to this effect, specific growth changes in sexual structures in the body are probably due to an abnormal production of adrenal secretion.

In making this review I have accepted, tentatively, the opinions of Grollman, particularly in explaining the adrenogenital syndrome. This is because it is the only theory found which attempts to explain all the known adrenal relations. It is appreciated that his point of view is not accepted by some competent endocrinologists and that there has not yet been time to verify all of the facts he has presented.

HISTORICAL CONSIDERATIONS

Credit for the first description of the adrenal glands must be given to Eustachius, who in 1563 reported their recognition. According to Engelbach, they were named by Riolanus in 1628. Due to fantastic interpretations of real or fancied anatomic relationships, early explanations of adrenal function seem childish or ridiculous to present-day readers. Grollman gives an interesting survey of some of these theories. They were supposed to be mere "pillars of the abdominal cavity, to help support the stomach," or to support neighboring nerve plexuses. It was stated that they had various relations to secretion through the kidney. Some stated that the blood was rendered non-coagulable by their action. The brownish blood frequently found in them at autopsy, and now recognized as a result of postmortem autolysis, was said to "give color to and animate the blood and produce fermentation of the heart." Severinus and Valsalva stumbled upon a relationship between adrenals and sex glands, based upon imagined ducts linking them together, but they had no inkling of the true relationship, the cause for which is even now debated. It was maintained by Senac that they secreted meconium, as well as a substance preventing renal calculi and a fat-producing substance.

Accessory adrenal tissue in various parts of the body was described by Morgagni, who also noted the relatively large size of the fetal glands. Along with Goodsir, he considered them to be of functional importance only in prenatal life. It was not until the nineteenth century and its active study of the comparative anatomy of glands that the idea of functional relationship between adrenals and kidneys lost ground and their true relationship to the nervous system began to be considered. Echer, in 1849, first demonstrated the glandular nature of the structures, and hypothecated that they must pour some secretion into the blood stream. Leydig, in 1853, demonstrated histologically their relationship to the sympathetic nervous system, and Arnold, in 1866, divided the gland into its conventional zones on the basis of his microscopic studies.

Our modern conception of adrenal function, however, may be said to date from Addison's classic description of the disease that bears his name, in 1855. This was followed quickly by the experimental work of Brown-Sequard, who demonstrated in 1856 that the adrenal glands were essential for life. Whereas all of his adrenalectomized animals died, improved technics, developed in later years, enabled various other experimenters to save from 15 to 20 per cent of the animals operated upon. We now realize that even these few remained alive by virtue of accessory adrenal tissue not removed by operation. In 1856 Colin and in 1865 Heule demonstrated the two different types of tissue with unlike staining reactions in the suprarenals. Wiesel, in 1904, described the chromaphil system as we know it now. Oliver and Schaefer, in 1894, reported that suprarenal extracts caused a rise in the blood pressure, and in 1896 Frankel isolated adrenalin. Abel crystallized it, and in 1901 Takamine and Aldrich perfected it for commercial use. The fact that the pressor substance was isolated from these glands before its more important growth or life-promoting hormone was discovered recalls similar experiences in the investigation of the pituitary gland. In this case pituitrin, another pressor substance, was known to exist long before its more important and specific growth hormones were suspected.

When it began to be evident from experimental work that it was the cortical rather than the medullary part which was essential for life, search for an active cortical hormone began, culminating in the isolation of cortin by Swingle and Pfiffner and by Hartman and his coworkers.

EMBRYOLOGY AND ANATOMY

The adrenal glands, like the pituitary, are composed of two parts, united from different types of tissue of entirely separate origin embryologically, the external, cortical or interrenal, part and the medullary or chromaphil portion. The physiologic reason for their union is still unknown. Indeed, in some of the lower fishes, the two types of tissue remain separate throughout life.

According to Grollman, interrenal cortical tissue has not been found "in animals below the Cyclosomata (hags and lampreys). Chromaphil or medullary tissue, however, has been demonstrated in animals as far down the scale as leeches. Only in mammals, birds, and reptiles are the two structures combined into one organ. Extracts of chromaphil tissue from lower animals have adrenalin-like, pressor or sympathomimetic activity. Also, removal of structures which have interrenal ap-

pearance, in animals below the level at which the two types of tissue are united into one organ, has produced death, with symptoms similar to those of cortical insufficiency. Only in mammals is the medulla completely surrounded by cortical tissue.

The adrenals in most animals weigh from 0.01 to 0.02 per cent of the total body weight, although in some, notably the guinea pig, they are relatively ten times as large. The adrenals increase in approximate proportion to the general body weight, except for the marked change which takes place soon after birth, to be spoken of later on.

The adrenals of wild animals in a species are said to be considerably larger than are those of domesticated types, indicating possibly, that the more hazardous life of the wild animals needs the added vigor and metabolic activity provided by more adrenal substance.

In human beings the size of the adrenals may vary from 5 to 15 gm. in the adult, usually being larger, if the person has died of a prolonged infection. The medulla comprises about 10 per cent of the bulk.

There is a separate arterial supply to the two parts of the gland, but there seems to be no well-developed venous system from the cortex, the secretion of which is probably drained into the veins of the medullary portion.

Embryologically, both interrenal and chromaphil tissue is differentiated very early, by the fourth week. The cortical cells develop from the ventral portion of the celomic epithelium, mesoderm, and the chromaphil cells find their origin from the neural crest, ectoderm. The presence of accessory adrenal bodies, in many instances widely spread throughout the abdominal and thoracic cavities, has complicated all of the experimental work done on these glands, because of the difficulty in removing all of these structures at operation. Such accessory bodies may contain either interrenal or chromaphil cells. It is now well recognized that the adrenal medulla is but the central portion of a widespread chromaphil system.

HISTOLOGY

The cortex is usually said to be divided into three zones, zona glomerulosa, beneath the capsule, in which the cells have an alveolar arrangement; zona fasciculata, with radially arranged cells rich in fats; and the zona reticularis, with its irregular arrangement, intimately interlaced with the edge of the medullary portion. These zones are poorly defined, and it is not believed that they have different functional significance. It is usually taught that new cells are formed at the glomerulofascicular junction. The glomerular zone is said to undergo considerable fatty change during pregnancy, so that it becomes almost identical in appearance with the fascicular region. The fascicular zone is narrow in childhood, but after puberty the columns of cells become longer, thickened, and more closely packed. This increase recedes later in life. The reticular zone increases in size throughout life and is characterized by its rich capillary network and the presence of pigment, which is thought, however, to have no relation to that of Addison's disease. It is in this zone that degeneration of cells takes place, hence its appearance changes with differences in the rate of new cell formation and cell destruction.

The medulla at the time of birth is a rather small, undifferentiated strip of tissue. Its development is almost entirely postnatal and takes

place at the time at which the extra-adrenal chromaphil system degenerates. The cells of the medulla are large polyhedral cells, arranged in an irregular network in a stroma of rich blood supply containing smooth muscle fibers and nonmedullated nerves.

The cortical region is particularly sensitive to degenerative changes due to faulty nutrition, toxins, or infections. In these conditions the reticular zone shows the most marked changes, and its degenerating cells are quickly replaced by new cell formation occurring in the outer zones. This fact, plus its extremely rapid postmortem autolysis, has made it difficult to evaluate the condition of the adrenal gland from postmortem material.

In human beings at birth there is a large zone between the reticularis and the medulla, which undergoes rapid involution during the first two weeks of life and is finally represented after the first year by a mere trace of cells, sometimes referred to as the "juxtamedullary zone." This is the part termed androgenic in Grollman's discussion, and, according to him, it is of great importance in various pathologic conditions having to do with masculinizing growth changes.

If this conception proves correct, it will explain the relation of the adrenals to the well-known adrenogenital syndrome. Grollman maintains that the cortex has two functional parts: the first, the one composed of interrenal tissue which produces the hormone, cortin, necessary for life and growth; and the androgenic tissue, responsible for a secretion which stimulates the genital system. This latter tissue develops in fetal life, reaching its maximum proportions at the time of birth. The relatively large size of the adrenals at this time, one-third that of the kidney, is due to the preponderance of this androgenic tissue. Accessory tissue of this type is found in other parts of the body, just as we find accessory deposits of interrenal and chromaphil structures.

According to Grollman's latest theory, the adrenals of newborn babies present an appearance markedly different from that seen in later life. The true cortex, interrenal tissue, exists as a narrow rim around the thick zone of androgenic tissue which comprises a greater part of the gland. The medulla exists as a strip on the interior of the gland. The involution of androgenic tissue, which begins soon after birth, becomes "massive" at two weeks of age, at which time the medulla, on the contrary, is undergoing its most rapid growth. During this period the androgenic zone is sharply demarcated from both cortex and medulla. The involution, almost complete at one month, is not entirely consummated until the age of three years and includes the disappearance of the accessory androgenic tissue, as well as of that in the adrenals. The small juxtamedullary strip of tissue, referred to above, according to Goormaghtigh and Grollman, is a remnant of this androgenic zone. When tumors arise from this zone, the virulizing changes seen in the genital system are found.

PHYSIOLOGY

Since the medulla secretes no hormone necessary for, or markedly influencing, growth, its activity will not be discussed. Results from operative experiments have shown that it is the cortex only which is necessary for life. Complete cauterization of the medulla of animals has not interfered with the maintenance of good health over long

periods of time. Some endocrinologists still feel, however, that "adrenal asthenia" is due to medullary hypofunction.

While the cortex is essential, it has been shown that relatively small amounts of tissue are sufficient for maintenance of life and that sometimes the extra-adrenal accessory tissue was adequate. In other cases, the survival period of animals has been prolonged by the presence of this accessory tissue, which has finally failed to function, resulting in ultimate death. In such instances, the accessory structures have been shown at autopsy to have undergone exhaustion atrophy. According to Banting and Gairns, the symptoms of cortical insufficiency are weakness, anorexia, low body temperature, low blood sugar, anuria, vomiting, diarrhea, convulsions, coma, and death from respiratory paralysis, the heart still beating after respiration fails. The muscular weakness and paralysis is not due to nerve failure, but probably results from changes in the chemistry of the muscles, the accumulation of lactic acid, or impoverishment of carbohydrate supply. Although the drop in blood pressure is terminal in deaths from adrenal insufficiency, the cardiac output is diminished early, and progressively. This may be due to blood concentration, following the marked loss of plasma in this condition.

Experimental deficient animals are hypersensitive to toxins and unable to maintain their body temperatures. Their muscles are easily fatigued and all reproductive functions are stopped.

Animals which die show pigmentation of the skin, dry tissue, condensation of the blood, absence of fatty tissue, reddening, ulceration, hemorrhage from the intestinal tract, degeneration of the liver, increase in the lipids in the tubules of the renal cortex, lymphatic and thymic hyperplasia, congestion of the pancreas, and other endocrine changes to be discussed later.

The chemical changes found in the blood are of great importance in understanding the physiology of the adrenals. The cholesterol content of the blood is markedly increased by adrenalectomy. This is probably due to decreased liver function. Similarly, the nonprotein nitrogen is elevated because of decreased renal function.

After the operation early diuresis sets in, causing a loss of water which is not replaced by normal thirst and producing a negative water balance. As a result, the blood plasma in animals is decreased about 8 to 10 per cent. Another factor in this water loss is probably an increase in the secretion of sodium chloride through the kidneys. Coincidentally, there is an increase in the blood concentration of potassium and magnesium, amounting to from 23 to 42 per cent in cats. This is partly retained from food, and partly extracted from the tissues. The potassium-sodium and potassium-calcium ratios are upset. Since more sodium is lost than chlorine, there results a decrease in the bicarbonate in the blood, leading to a relative acidosis and the common symptom of hyperpnea. In addition to these chemical changes, there is also an hypoglycemia, due to liver damage. The animal, in severe adrenal insufficiency, therefore suffers from marked dehydration, disturbance in the blood electrolyte balance, acidosis, and hypoglycemia. The administration of water and sodium chloride orally or parenterally serves to lessen the symptoms but does not permit life or growth to go on indefinitely. The relation of the suprarenals to the glucose metabolism is complicated. It is probable that under normal conditions the medullary secretion, under pancreatic control, stimulates the liver, causing

the liberation of glycogen. With cortical insufficiency the ensuing liver damage causes decreased production of glycogen from this organ, even when medullary secretion is adequate.

While the basal metabolic rate is very slightly affected by the secretion of epinephrine and its general action on the tissues, a deficiency of cortin secretion markedly reduces the rate, resulting in a lowered body temperature and a decrease in the oxygen consumption. With sudden nonfatal adrenal injury, an initial increase in the basal metabolic rate has been noted, possibly the result of thyroid response.

RELATIONS WITH OTHER ENDOCRINE GLANDS

Pituitary.—Hypophysectomy causes an atrophy of the adrenal cortex to about one-fifth its normal size. On the other hand, in adrenal cortical insufficiency the basophilic cells tend to disappear, and there is a decrease in pituitary function. Neither gland, then, can supplant the other. It is probable that the immediate stoppage in growth in adrenalectomy may be due to secondary pituitary deficiency. The impotence observed along with the atrophy of the reproductive system after adrenalectomy is not relieved by cortin and is, therefore, believed to be a secondary pituitary result also.

Thyroid.—When both thyroid and adrenals are removed, the resulting low basal metabolism rate is not increased by the administration of cortin. No intimate relation with the thyroid has been conclusively demonstrated. This is also true of the *parathyroids.*

Gonads.—The adrenogenital syndrome, virilism, is due to androgenic tumor or hypertrophy, not to abnormalities of the medulla or interrenal tissue. The genital atrophy in cortical insufficiency is due to secondary effects from the pituitary.

Pancreas.—Cortical dysfunction decreases the carbohydrate supply through its damage to the liver. The pancreas is said to exert a controlling influence over the medulla which stimulates glycogenolysis.

Thymus and Lymphatic System.—There seems to be a reciprocal relationship between the adrenals and these structures, the reason or explanation for which is not at the present time clear.

CLINICAL IMPLICATIONS

Addison's Disease.—While this condition is extremely rare in childhood, when it does occur, it produces marked reduction in growth. This disease occurs preponderantly in males (two-thirds of the cases) and is characterized by pigmentation of the skin, cardiac and muscular weakness, low blood pressure, lymphoid hyperplasia, decrease in the eosin and basophiles of the pituitary, and sexual atrophy.

It seems possible that subclinical instances of cortical insufficiency may occur and account for some of the rarer conditions seen in childhood, in which asthenia, muscular weakness, and low basal metabolic rate are found. It may be that with experimental use of cortin and our more active interest in this subject more will be discovered along this line. Certainly, most of us in the past have seen children, who might have been benefited by such experiments. If preparations of cortin adsorbed on charcoal become available for oral administration, this line of investigation will be furthered.

Medullary Tumors.—There are several types of primary tumors arising from the medulla, none of which, however, give rise to growth changes.

Cortical Tumors.—According to Grollman, cortical tumors give rise to no symptoms from overproduction of cortin. Whether this is due to the fact that the hormone is very easily oxidized in the body, or whether it is not produced in abnormally large amounts in such tumors, is not known.

Androgenic Tumors.—Tumors of this tissue are found when the adrenogenital syndrome, masculinization phenomenon, is present. This occurs rarely in male children, never in adult men. It usually comes on early in life, at about two years of age, and leads to the development of secondary male sex characteristics, including enlargement of the penis or clitoris, masculine type of hair growth, and, rarely, increase in the size of the ovaries and uterus. Menstruation is not established in girls, and the testes remain infantile in boys. The muscular development is marked, giving rise to the "infant Hercules" with his adult appearance. It must be remembered that, since there is no actual functional sex maturity, this is not a true precocious puberty, such as is described in the similar syndrome associated with pineal tumors. Since this condition is due to a tumor of the androgenic tissue, surgical intervention gives the only hope for cure. Those who have had experience with this syndrome, speak of the likelihood that only one adrenal gland may be found present in the body and, therefore, advise exploration of the opposite side before removal of the pathologic adrenal. In the event that there is but one gland, partial removal, or complete removal with transplant becomes necessary. The *adrenal virilism*, which occurs in adults, is limited to females and occurs in early adolescence or at the menopause. It is characterized by the male type of hirsutism, psychologic outlook, body contour, and voice. While the clitoris hypertrophies, other female organs may atrophy. The tumor is usually bilateral, and its surgical removal in one or two stages gives a relatively good outlook.

Adrenals and Hermaphroditism.—That there is some relationship between the adrenals and hermaphroditism has long been known. The fact of embryonic bisexuality is evidenced by the coexistence of müllerian, female, and wolffian, male, ducts. In normal female development the wolffian ducts disappear, but their persistence, in other cases, may lead to "tubular hermaphroditism," in which condition secondary male characteristics exist with female generative organs. Grollman hypothecates that the androgenic zone of the adrenals is hypertrophied in this type of pseudohermaphroditism. He refers to the work of Gallais, Wiesel, and Glynn, who note the common origin of gonads and adrenal cortex and mention that the ovary is hermaphroditic in its original structure. It is the male medullary part of the beginning ovary which is closely related to the origin of the adrenals.

Cushing's Disease.—This disease, previously said to follow basophilic tumor of the anterior pituitary, has recently been described in cases in which hyperplasia of the adrenals (presumably of the androgenic tissue) has been the only lesion found at autopsy. This fact, coupled with the observation that there is some relation between the adrenals and the basophilic cells of the pituitary, makes it seem possible that a revision of our knowledge about the cause of this syndrome will be

necessary before it can be evaluated adequately. Grollman believes that a similar condition, the "diabetes of bearded women," is due to androgenic hyperplasia.

Anencephaly.—Hypoplasia of the adrenal glands has been an almost constant observation in anencephaly. These hypoplastic glands, however, are normal, except for the absence of the androgenic zone. Since this zone is, according to one hypothesis, a part of the reproductive system, its absence could be explained by the lack of pituitary stimulation, resulting from anencephaly.

Status Lymphaticus.—Many authors have noted the reciprocal relationship between the adrenal cortex and status lymphaticus, in which condition hypoplastic adrenals are found. It is quite possible that future work may clarify this relationship and explain much that we would like to know about this controversial condition.

Hemorrhage Into the Adrenals.—Consideration of the clinical implications related to the adrenals is not complete without mentioning hemorrhage into these glands during the neonatal period. It has been found that small hemorrhages into the androgenic zone are so common as to be considered almost normal. It is quite possible that increase in the severity of these hemorrhages may be induced by birth or other trauma, resulting in lesions serious enough to account for death in the first days of life.

Hyperfunction of the adrenals except in the conditions named above is not important, because the cortical hormone is quickly oxidized when produced in excess.

Both cortex and medulla contain *Vitamin C* in the proportion of 3 to 2. It is not known that this has any growth implication.

The presence of a *lactating hormone* in the adrenals has been reported, but has not yet been isolated.

SUMMARY

The adrenals secrete two known hormones and probably two others as yet not isolated. The first, suprarenin from the medulla, is intimately associated with the sympathetic nervous system and the carbohydrate metabolism but is not directly related to growth. The other known hormone, cortin, is necessary for life and growth. The hypothecated internal secretion of the androgenic zone has a definite masculinizing effect on growth, and the lactating hormone, if present, has a definite growth relation.

More seems to be known about body chemical changes in cortical insufficiency than about such effects from any other endocrine lesion. Perfection of oral methods of administration of cortin might lead to important discoveries in the way of body chemical control.

The Parathyroid Glands and Growth

Although the external parathyroid glands were first described in 1880, little was known concerning their function or the relationship of these glands to growth and development until a quarter of a century or more later, when for the first time experimental work revealed the importance of their secretion to the calcium and phosphorus metabolism of the body and the relation to the bony development and the nerve and muscle tone.

HISTORICAL

Sandstrom is recognized as the first person to describe the external parathyroid bodies. He did this in 1880, but it was not until fifteen years later, in 1895, that the internal pair of glands were discovered and described by Kohn. The real significance of these structures remained unknown until 1908 when MacCallum and Voegtlin first called attention to certain nervous reactions following parathyroidectomy and their relation to serum calcium levels. Years before this time and even before the parathyroids had first been found and described, one may find in the literature various references to peculiar reactions and death in animals following thyroidectomy. The parathyroids had also been removed unwittingly. Earlier descriptions of the glands were forgotten and overlooked until finally, in 1891, Gley independently rediscovered the external glands. Immediately, workers began to investigate the effects of the removal of these bodies, but the results were not consistent or in agreement. They were not aware that other pairs of these glands often existed, and it was not until after 1895 when Kohn described the internal pair that experimental results began to be more in agreement. Even then aberrant glands located in positions often far removed from those where parathyroid tissue is normally found would confuse the observations. In spite of these difficulties Vassale and Generali in 1900 demonstrated that tetany in cats and dogs was the result of parathyroidectomy. They further showed that thyroidectomy had nothing to do with the production of tetany if the parathyroids were left intact. This work in particular gave strong impetus to a large amount of experimental work by many investigators. Many of their results must be discounted, however, because possible aberrant glands were not searched out and removed.

In 1924 Berman, Hanson, and Collip, all working independently, were able to isolate the active principle of the parathyroid glands. Investigators working with that extract have now, of course, been able to give us a much clearer conception of the function of these glands and their relation to the various activities of the body.

EMBRYOLOGY AND ANATOMY

The parathyroid glands are found in all vertebrates except fish. They are small bean-shaped bodies, usually four in number, which lie in close association with the posterior surface of the thyroid gland. They are brownish red in color and are usually described as superior and inferior pairs; the superior, or internal, pair often is found imbedded in the thyroid. The average weight in adults is from 35 to 55 mg., and in children the gland is about one-fourth of the adult size. In the fetus they are first distinguishable at about the fourth month. The glands arise as paired structures from the third and fourth branchial clefts. Herrman, following dissection of many specimens, revealed a new anatomic concept of these glands. He describes the glands as arising from "stalks," four in number. One pair is formed by the junction of the inferior thyroid artery and a branch of the recurrent laryngeal nerve; the other pair by a branch of the superior thyroid artery and a branch from the superior laryngeal nerve. He believes that from any stalk two or more parathyroid glands may arise.

Aberrant glands are not uncommon. These may be found near the principal glands but often are found imbedded in the thymus or the thyroid. They have also been found far removed from their usual location and may be in the mediastinum and the areolar tissue about the pericardium. One readily perceives that these aberrant glands may exert a very important influence when factors concerned in the treatment of parathyroid dysfunction are considered. As previously mentioned, many an experiment concerning the effect of parathyroidectomy in animals must be discounted because the worker failed to remove these glands or failed to consider the possibility of their influence upon his results.

HISTOLOGY

Two types of cells are found in the structure of the encapsulated gland. These cells are separated into clumps by fibrous connective tissue. The principal, or chief, cells are large and clear with vesicular nuclei and faint staining cytoplasm. The second are the large oxyphil cells. These have a centrally placed, small, oval, deep staining nucleus. A third group of cells has been described, and these are known as the small dark cells. Very little is known about the difference in function of these three types of cells, but their presence suggests that the parathyroid gland may have more than one function.

PHYSIOLOGY

The parathyroid glands function prominently in the process of growth and development, for their rôle in calcium-phosphorus metabolism is important. The development of normal structure in bones and teeth and the maintenance of normal states of nerve and muscle tone probably depend to a large extent upon the normal functioning of these glands. With the isolation of the active parathyroid principle in 1924, experimental work took on new significance and importance, for the specific effect of this extract upon animals could be accurately observed. Various workers soon established the fact that intramuscular or subcutaneous injection of the hormone produced a rise in the serum calcium levels. They observed further that its use produced diuresis and that an increased excretion of calcium and phosphorus took place. Jaffe, Bodansky, and other workers then reported that daily injections of the hormone caused resorption of the spongy and cortical portions of the bones and that fibrosis and giant cell tumor formation occurred. These observations were made in experiments with dogs, and it is now known that an almost identical reaction occurs in human beings. *Osteitis fibrosa cystica*, or von Recklinghausen's disease, was then, for the first time, recognized to be definitely the result of disturbed parathyroid function. Other factors, too, such as the reserves of water and electrolytes, play a part in the diuresis and excretion of calcium and phosphorus. Shelling believes that diuresis is impossible unless optimal reserves of these are present.

Deficient parathyroid secretion may result in diminished concentration of calcium and phosphorus in the blood, and this condition in turn causes the clinical state known as *tetany*. There is a close, but inconstant, relationship between the severity of tetany and the serum calcium level. The fact that this relationship is not constant suggests to Shelling that another factor plays a part, and this he believes to be the inorganic phosphorus. He points out that in hypoparathyroidism

there is hypocalcemia, hyperphosphatemia, decreased excretion of lime salts in the urine, and a retention of calcium and phosphorus; while in hyperparathyroidism there is hypercalcemia, hypophosphatemia, increased excretion of lime salts, especially in the urine, and a negative calcium balance.

The exact relationship between the parathyroids and calcium-phosphorus metabolism is still undecided. Goodby and Stacey believe that the phosphate diuresis following injection of parathormone "results from direct action in the kidney and is not causally related to hypercalcemia." Collip, Pugsley, and Selze say: "The characteristic effect of the parathyroid on the bones of rats is obtainable after bilateral nephrectomy and hence cannot be ascribed to an action of the hormone on the renal threshold for phosphate." Tweedy and Templeton report that, according to calcium values and microscopic observations, parathyroid extract is ineffective in bilaterally nephrectomized dogs, but a unilaterally nephrectomized animal reacts in a manner comparable to a normal dog. Coppo and Pisa believe that they have found a direct relationship between the function of the parathyroids and the biochemistry of magnesium. Ellsworth and Nicholson suggest that the hormone tends to increase the output of base, particularly sodium. Combs, Pike, and Searle suggest that the source of excreted calcium may be in part, or entirely, the striated muscles and that the speed of metabolic processes in the muscles determines the time various symptoms will develop following parathyroidectomy. Other workers suggest that parathyroid dysfunction may result in the production of toxic amounts of methyl guanadine. This substance is produced by the action of phosphoric acid on creatine. Margaret Hoskins in recent work with parathyroidectomized rats concludes that a low serum calcium is a necessary part of the tetany syndrome but that the development of symptoms depends also on other endogenous factors, the nature of which is not known.

These various reports are mentioned in order to emphasize the fact that the exact function of the parathyroid and its relation to other body processes is not entirely clear.

The relationship of the parathyroids and vitamin D is of great interest in reference to growth and development. There is evidence to indicate that vitamin D stimulates the gland to greater activity while other work suggests that the parathyroids are not necessary for the activity of vitamin D. Kozelka, Hart, and Bohrstedt report that dogs with ablated parathyroids were able to live on without development of tetany, would grow normally, and would have normal estrus and successful gestation and lactation provided the calcium level was adequately controlled by administering vitamin D. Shelling points out that from the standpoint of calcium and phosphorus metabolism the effects of vitamin D and parathyroid hormone differ. Therapeutic amounts of vitamin D cause a positive balance of calcium and phosphorus if rickets is present, and this produces a healing in the metaphysis of bones, while parathyroid hormone causes a negative balance and a retardation of ossification. Other workers believe that rickets can be prevented or cured by either substance, and still others believe there is a diversity of action between the two substances and that their activities are quite dissimilar. It is at least quite probable that a proper balance of calcium, phosphorus, and vitamin D is necessary to

produce normal ossification, and it is quite possible that vitamin D and parathyroid hormone may work together to maintain that balance. The way in which they cooperate remains to be discovered.

INTERRELATIONSHIP WITH OTHER ENDOCRINE GLANDS

Thyroid.—The relationship of the thyroid and parathyroid is not entirely clear, but they are believed to have some reciprocal action. Earlier workers believed their action to be antagonistic. Albright and Bauer have recently reported that thyroid medication in hypoparathyroidism raises the serum calcium, increases calcium excretion in the urine, increases the phosphorus excretion in the urine, but does not affect the blood phosphorus.

Thymus.—The relationship between the thymus and parathyroids is not known. Reports are available to show that the thymus and parathyroids are synergistic in their action; others, that they are antagonistic; and still others, that they have no relationship.

Hypophysis.—The relationship between the pituitary and the parathyroids is difficult to determine, owing to the many functions of the pituitary gland. Much work has been done and is in progress concerning this problem. Hoffman and Herold conclude that the parathyroid is stimulated by a parathyrotropic substance in the anterior lobe of the hypophysis. Hoffman and Anselmino report that an extract of the anterior lobe of the hypophysis affects the blood calcium through the medium of the parathyroid. Other workers believe that hyperparathyroidism may possibly be due to an involvement of the anterior pituitary basophilic cells. Hertz and Kranes and also Anselmino and Hoffman have demonstrated that anterior lobe extracts of the pituitary gland will produce hyperplasia of the parathyroids. Albright and Bloomberg also believe that hyperplasia of the parathyroids is possibly caused by a stimulating factor derived from the anterior lobe of the pituitary.

Adrenals.—Again nothing definite is known concerning the relationship of the adrenals and the parathyroids.

Pancreas.—A considerable amount of experimental work leads one to believe that the secretions of the pancreas and the parathyroids have some synergistic action. Clinically the relationship is not clear. Several workers have noticed degenerative changes in the parathyroids following pancreatectomy in dogs. These changes were often accompanied by a decrease in the blood calcium and a rise in the plasma phosphates. Other workers have noticed that parathyroid extract produces an increase in the tolerance for carbohydrates. Shelling points out that clinically, the synergistic action of the two extracts is not easy to demonstrate because hypoglycemia is seldom found in uncomplicated hyperparathyroidism and in both tetany and hyperparathyroidism histologic changes in the pancreas are uncommon. Root, White, and Marble call attention to calcium metabolism disturbances in diabetes, such as spontaneous fractures, calcification of the arteries, decalcification of the teeth, etc., but it is possible that these phenomena are due to a deficient diet.

Gonads.—Again little is known concerning the relationship of these glands and the parathyroids. Possibly the sex hormones may influence the parathyroids through the anterior pituitary gland. During menstruation there is little detectable difference in the calcium and phos-

phorus levels, although clinically it has been noticed that attacks of acute tetany are frequently associated with the menstrual cycle in women. Men seldom have tetany. McCullagh and Kearns believe the sex glands have a pronounced effect upon the neuromuscular excitability in human parathyroid tetany. However, they found that variations in the amounts of sex hormones in the body were not correlated with alterations in the serum calcium and phosphorus levels. They believe that these hormones must affect the neuromuscular excitability through a different mechanism. Among animals deprived of the parathyroid gland, tetany is much more easily produced by lactation than by either pregnancy or estrus.

CLINICAL IMPLICATIONS

The clinical significance of the parathyroid glands, of course, could not be fully appreciated until the hormone was first isolated in 1924. Since that time information gathered from many experiments with the extract has enabled the physician to understand better many puzzling clinical findings which had hitherto defied explanation.

Osteitis fibrosa cystica, or von Recklinghausen's disease, has been recognized only since 1925 as the probable result of hyperparathyroidism. Although this disease is rare in childhood, cases have been reported in children as young as two and one-half years. This affliction is usually characterized by an insidious onset with pain in the lower back and extremities, lassitude, and hypotonia. At this stage it is often mistaken for rheumatism. Thus an individual having these symptoms, in whom rheumatism is suspected but not proved, should be placed under observation with the thought in mind that early osteitis fibrosa cystica may exist. Serum calcium and phosphorus determinations should be done, and x-ray observations should be made to detect early bone changes.

Renal rickets may be confused with more advanced von Recklinghausen's disease, but in this affliction renal damage usually precedes bone changes. However, if the osteitis fibrosa cystica has progressed to the stage where kidney damage has occurred, one may find it extremely difficult to make a correct diagnosis. Hypertrophy of the parathyroid glands has been so commonly observed in many cases of renal rickets that Park and Eliot suggest that the disease would be more accurately described as renal hyperparathyroidism. A careful history is important in order to differentiate the two diseases. In renal rickets impaired kidney function may exist without occurrence of nephrolithiasis or nephrocalcinosis, while both conditions are usually found in hyperparathyroidism.

Fractures and marked deformities of the long bones appear in more advanced stages of von Recklinghausen's disease and practically all bones of the body will reveal x-ray evidence of demineralization. Different observers have suggested that mild degrees of hyperparathyroidism might account for certain clinical findings which seem to exist alone. Among these are *nephrolithiasis*, *nephrocalcinosis*, and mild degrees of *osteoporosis*, *chronic rheumatic polyarthritis*, and *spondyloarthritis*. However, no definite evidence can be established to prove that hyperparathyroidism is the cause of these afflictions. The osteoporosis of hyperthyroidism, or of pituitary basophilism, should not be confused with von Recklinghausen's disease. Nor should osteogenesis

imperfecta, Paget's disease, osteomalacia, xanthomatosis generalista ossium, and other disorders which may be mistaken for and have often been ascribed to hyperparathyroidism.

The cause of *hyperparathyroidism* is unknown, except that it is believed that the renal damage in renal rickets results in the hypertrophy of the glands often found in this disease. The most satisfactory treatment for hyperparathyroidism is parathyroidectomy. Recently some benefit has been claimed from x-ray treatments. Dietary treatment (high calcium and vitamin D diets) has been used with indifferent success.

Hypoparathyroidism is of particular interest to the pediatrician. Although we know that deficient parathyroid secretion will usually result in impaired calcium and phosphorus balances and eventually tetany, no one as far as I can learn has yet conclusively proved a case of idiopathic hypoparathyroidism in childhood. Various nervous conditions in childhood are often said to be the result of improper calcium balance. More often than not the calcium and phosphorus levels are found to be normal in these disturbances. Children who present signs of incipient or advanced tetany respond very well to a diet which includes an adequate calcium intake and a proper balance of calcium and phosphorus, together with adequate amounts of vitamin D. Although parathyroid hormone is effective in the treatment of the convulsions of tetany, its use is rarely, if ever, necessary except as an emergency measure.

As Shelling points out, in the arrangement of high calcium diets one should be certain that foods having high phosphorus as well as high calcium contents are not too freely used, for high phosphorus content will hinder the use of the calcium. Milk and cheese are two foods which, although ordinarily thought of as high calcium foods and often presented in large amounts in calcium deficiency, are also high phosphorus foods. We have pointed out earlier that if the phosphorus quotient in the diet is too high, normal use of calcium is interfered with, and inversely, if the proportion of calcium is too high, increased excretion of calcium through the intestine occurs. This has been demonstrated repeatedly in animals. Thus if a diet is given which maintains the calcium-phosphorus ratio at about 1 to 1, no change in the bones appears. However, if calcium is increased so that the ratio is about 4 to 1, severe rickets develops. During recent years there has been considerable ill-advised use of calcium therapy without an understanding of how the whole metabolic process of calcium and phosphorus works. Many children have probably been given large doses of calcium in efforts to relieve what are believed to be signs of calcium deficiency without consideration of the fact that the important calcium-phosphorus balance may be upset thereby. As a result, the child is really robbed of lime salts by an increased excretion of them through the bowel in the form of insoluble calcium phosphate. Hypercalcemia does not necessarily mean that lime salts are being laid down in the body, for it may be that they are actually being removed. Shelling definitely states that in most instances hypercalcemia indicates a loss of calcium from the bones to the excretory channels.

Parathormone therapy has been used in the treatment of a long list of disorders, but it must be emphasized that its use is superfluous in most of them and not without danger. In practically every instance in which its use seems indicated, identical results can be obtained by

proper diet and the use of vitamin D. This is even true in most cases of hypoparathyroidism, and the use of the hormone, according to most authors, is indicated only as an emergency measure in the control of active or impending tetany.

SUMMARY

The parathyroid glands, which are structures anatomically located in close relationship to the thyroid gland, have an important function in the calcium-phosphorus metabolism of the body. Partially because of the comparatively recent isolation of their hormone, little is known concerning their true relationship to the other glands of internal secretion of the body. Derangement of their function with resultant hypersecretion, or hyposecretion, is followed by distinct trains of symptoms and changes in body function in which bone lesions and nervous reactions are prominent. In these the derangement of the normal calcium-phosphorus balance is the immediate cause. Specifically the parathyroid hormone increases the serum calcium level and will mobilize calcium from any body tissue where it is available.

Certain workers believe that parathyroid function can be entirely supplanted by the use of vitamin D and proper diet. This theory has not been definitely proved, and there is reason to doubt that it is true. Clinically, it is true that symptoms of hypoparathyroidism usually can be relieved by administration of vitamin D and proper diet.

Indiscriminate calcium therapy may be and often is dangerous to the patient. Hypercalcemia does not necessarily mean that adequate calcium is being supplied to the tissues. Actually it may be on the way out, and demineralization of the body may be taking place.

REFERENCES

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American Academy of Pediatrics

Proceedings

ANNUAL MEETING OF REGION II OF THE AMERICAN ACADEMY OF PEDIATRICS

The meeting was held at the Belvedere Hotel, Baltimore, Md., November 16, 1936. Dr. Edward C. Mitchell, Memphis, chairman of Region II, presided.

CHAIRMAN MITCHELL.—Since this is the beginning of my second term as regional chairman, I will open the meeting by enumerating a few of the trials and tribulations of this office. The state chairmen are cooperating a little better each year, and, perhaps when my successor takes office four years hence, everything will run quite smoothly. One of my chief difficulties regards applications for new membership. It is necessary that each of these applications be passed on in my office before being sent to members of the regional board for approval. The application is then sent to Dr. Grulee's office, and each member of the Academy in this region is given an opportunity to express an opinion regarding the applicant. This is relatively impossible when the applications are received only one week before the regional or annual meeting and necessitates holding the applications over for six months. Often because of this the applicant is very much perturbed. If state chairmen would notify the members in their states that applications should be sent in at least two months prior to the meeting, they would confer a great favor on this office.

This year the reports of the state chairmen as well as all regional matters for discussion, have been mimeographed in sufficient quantities so that each member may have a copy.

The first subject for discussion is the next regional meeting. As you know, at the present time we are having considerable difficulty with the American Medical Association, the Southern Medical Association and various of the state societies, with regard to the time and place of the Academy meetings. Both the national and the local groups object to our meetings being immediately before theirs because it limits the attendance at both gatherings. The claim is made, and rightly so, that many pediatricians come to the Academy meeting and leave before the meeting of the Section.

A suggestion has been made regarding the Southern Medical Association that we have our next regional meeting at the same time and on the same days that the Section meets. Next year should the Pediatric Section of the Southern Medical Association meet in the morning, our meetings would come in the afternoon, our business meeting being held, probably, at an evening session.

As the Pediatric Section of the Southern Medical Society presents papers, it has been suggested that we have one series of round tables and on the following day clinical presentations similar to the ones we have had at this session.

The motion was made and seconded that the meetings be carried on jointly.

CHAIRMAN MITCHELL.—I would suggest that a committee be appointed to confer with the council of the Southern Medical Association and to arrange a time for each meeting.

A motion was made to this effect, seconded, then passed.

CHAIRMAN MITCHELL.—I appoint the following committee: Dr. Hugh Leslie Moore, chairman, Dr. Harvey F. Garrison, and Dr. Alfred A. Walker.

CHAIRMAN MITCHELL.—I now suggest a motion regarding the type of meeting.

DR. ALBERT ROOT (RALEIGH).—I move that we discuss clinical questions such as we had today.

This motion was seconded and passed.

CHAIRMAN MITCHELL.—I appoint the following committee to determine the type of meeting and be in charge of all arrangements: Dr. Wilburt C. Davison, chairman, Dr. Horton Casparis, and Dr. Aldert Root.

At this time I should like to appoint Dr. L. R. DeBuys, chairman of a local arrangement committee; the other members of this committee to be named by him.

I wish to draw attention to the fact that there seems to be an erroneous impression as to the method of selecting members. The regional chairman is the only member of the Academy who has no vote. His routine is to accept the verdict of the state chairman as to all applications in his state. This region has adhered to the policy of admitting only those candidates who limit their work to pediatrics. This differs some from the other regions. When I receive an objection to an applicant, I immediately write the state chairman, and his opinion is accepted as final.

The next order of business will be a report of the committee appointed to survey the children's hospitals of this region.

DR. W. C. DAVISON, (DURHAM) (Committee Chairman).—The following report will be submitted to the chairman in brief:

The Committee obtained information on 194 hospitals, and they expect answers from 32 additional ones in the next week or two. It was noted that in this region there are over 5,000 beds available for training pediatric internes. In addition to 194 hospitals, there are 10 exclusively children's hospitals, yet many men in our region must receive their training in New York and Philadelphia when the same may be available here. Inquiries are being made to find out how we can have more opportunities for training in this field.

CHAIRMAN MITCHELL.—As this finishes the order of business, we will next call upon the national president of the Academy, Dr. L. R. DeBuys.

DR. DEBUYS (NEW ORLEANS).—I think Region II has done itself honor in its numbers at this meeting. The thought came to me in discussing whether we should meet with the Southern Medical Association, that it must be remembered that we are members of the Academy, and that we are also members of the Southern Medical Association and should not sacrifice either one of the organizations. We cannot subordinate this to the S. M. A., nor do we want to see the S. M. A. sacrificed. I think whatever we do is going to be an experiment. We do not want the S. M. A. to feel that we are the tail—that they are the wag. Nor do we want to wag the tail. It is easier for us to come from home and attend both meetings, when we consider our own comfort. I do not know what is the best thing to do, but let us think of ourselves as a dual personality. The Academy is going to do more in directing us in things pediatric, and the greater the strength we create, the greater respect the other organizations will have for us.

CHAIRMAN MITCHELL.—We are five years old, and we have 200 members in this region alone. Some of the states have admitted all of the men eligible in the state. All of the states have done well. All of the states in this region have pediatric societies which function. One weakness is there are not enough members in the Academy actively engaged in Academy work. The state chairman is doing

all of the work in the state. Dr. Roberts has started a subcommittee of his "National Committee on Child Health Relations." Why could not other national committees be so utilized and each State Chairman subdivide his work so that each member might feel he had an active part in Academy work? I was speaking with a member of one of the older organizations, similar in character to this one, and he made the statement that he felt it was no honor to belong to the organization, but, if he did not belong, he would be criticized. We do not wish the Academy to be considered in this light. As I have said before, the Academy is now five years old; its growth has been remarkable. Such development could have been possible only as the result of personal supervision. We have with us tonight the man who at a sacrifice of his own personal affairs has given his time and energy to the American Academy of Pediatrics. This man is, indeed, responsible for the rapid growth of this organization, our secretary, Dr. Grulee.

DR. CLIFFORD G. GRULEE (EVANSTON).—We need cooperation with known medical organizations, radio programs, and Parent-Teacher Associations, with a definite outline regarding school health and school health education. The committee is active. It is putting out a questionnaire for state chairmen at least, and will probably send it to each member of the organization. I believe the southern states are organized better than those of any other section. The regional chairman and state chairmen are active. I wish the rest of the groups were as well organized. It takes time to make an organization successful; it takes a long time to weed out and get the right men. We are looking for men who will do a good job. It is hard to get the men. You hear a great deal about equipment, but I believe personnel is the important thing. We have an active organization, and by next year we will probably have 1,200 members. After July 1 we cannot take anybody who has not passed the Board of Pediatrics. Do not be discouraged by Dr. Davison's report of the hospitals. The best situation is in Region I. Some of you can look back on pediatrics twenty-five years ago and see the great advance made in pediatrics in those twenty-five years. In a first-class medical school, pediatrics is one of the four important subjects in the curriculum because the men have worked together. Now the medical profession recognizes pediatrics.

CHAIRMAN MITCHELL.—In closing I wish to express my appreciation for the honor of being reelected regional chairman for another four years. I am here to serve you at any time. I would suggest further that the members of this region by a rising vote express their appreciation to the members of Region I for the splendid meeting in Baltimore, also to the Baltimore members, and especially the local chairman, Dr. Fred Smith, for their gracious hospitality.

Reports Received Since Business Session

Dr. H. Leslie Moore, Dr. Harvey F. Garrison, and Dr. Alfred A. Walker, committee appointed to confer with the council of the Southern Medical Association as to the time of the regional meeting for next year, report that the council of the Southern Medical Association were in favor of the idea of holding the meeting of the Academy jointly with the meeting of the Pediatric Section, the Academy meeting to be in the afternoon and that of the Section in the morning.

The meeting is to be in the form of round table discussions the first day; with clinical presentations by the physicians of New Orleans the second day. The business meeting will be on the evening of the first day.

At the suggestion of both organizations this method is to be given a trial for one year, the future policy to depend entirely upon the result of this meeting.

At a subsequent meeting, the committee to determine the type of meeting, Dr. Wilburt C. Davison, Dr. Horton Casparis, and Dr. Aldert Root, reported that the type

of meeting agreed upon jointly by the council of the Southern Medical Association and the committee of the Academy meets with their approval. Further suggestion was made that five round table discussions be given on the first day of the meeting, subjects and leaders to be reported later.

Annual Report of Activities of Region II (1935 to 1936)

Regional Board: Dr. E. C. Mitchell, Chairman, Dr. W. C. Davison, Dr. Hugh L. Moore, and Dr. William Weston

Region II:	Members as of January 1, 1936	202
	New members	4
	Applications pending	12
	Total pediatricians in region	825
	Number limiting their work in region	385

Before beginning this report, I wish to express my appreciation for the confidence you have shown by reelecting me regional chairman for the second term.

In the past much time was consumed by reading the reports of the state chairmen; as a result there was not sufficient time left for full discussion. For this reason this year at the suggestion of your national president, Dr. L. R. DeBuys, I am giving each member a mimeographed copy of these reports, together with an outline of the current problems I feel should be fully discussed by all members.

On June 24, 1936, I sent to each state chairman a request that they discuss the following points with the members of their respective states and embody the results of this discussion in their reports:

1. The type of meeting you most prefer (go into detail).
   a. Annual meeting
   b. Regional meeting
2. If possible, find out from the members which round tables they like most, which they think can be dropped. If they have any suggestions as to new subjects they would like discussed at the round tables, let me know.
3. How many panel discussions and on what subjects would you suggest for the year?
4. Do the men as a rule like the innovation of having the two best pediatric papers of the year presented?
5. The suggestion has been made that in 1937 when we meet with the Southern Medical Association our sessions alternate with the sessions of the Pediatric Section of the S. M. A. As they have a morning session next year, our meetings would come in the afternoon.
6. There should also be discussion of the yearly meeting with reference to the relationship both as to time and place of meeting of the American Medical Association.
7. Although too many meetings work a hardship, it appears from the reports that in many states there has never been a meeting of the Academy; perhaps discussion of the advisability of getting together at least once a year might be of value.

Reports of State Chairmen

Alabama.—	Members as of January 1, 1936	11
	New members—1936	1
	Applications pending	1
	Total pediatricians in state	59
	Number limiting their work	27

When questionnaire arrived, I began to question the men and have been able to talk to most of them. I have not found anyone who thought that the meetings could be improved upon except for point 4. The feeling in regard to the reading of the best papers is that it is a duplication, as most of the men have already read that paper.

There was in Kansas City some discussion of the plan of having the Academy meetings at a time and place other than the meetings of the American Medical Association, and the men I have talked to are as hostile to the idea as the American Medical Association appears to be to our present plan. Alternating with either the S. M. A. or the A. M. A. section meetings is agreeable to most of the men.

Our members have attended so few meetings that they have no suggestions for a change in the round tables. I have attended more than any of the other men and have liked them; I have nothing but praise.

—Clifford L. Lamar.

Arkansas.—Members as of January 1, 1936	4
New members	0
Applications pending	2
Total pediatricians in state	29
Number limiting their work	5

I have consulted all but one of the members, and they feel that you get more from the regional meetings. It would be wise to have a general meeting about every third year, we think, for by that method there will be more close association of the members. If the general meeting could be held some place not too far from the center of the membership, the general meeting could largely take the place of the regional meeting.

The members felt that the round tables should be left largely to the program committee. The type of round tables they have had heretofore have given complete satisfaction. They seem to want the more usual rather than the unusual diseases discussed.

One morning or afternoon devoted to panel discussions would be their choice. They wish to have the plan of having the two best pediatric papers of the year continued. We feel that the Committee should work out program so far as possible in harmony with the Southern Medical Association and American Medical Association pediatric groups.

The Arkansas State Pediatric Society held its annual meeting in April at Hot Springs on the Monday morning preceding the meeting of the state medical society.

The speakers were as follows: Dr. Robert A. Strong, New Orleans, "Care of the Newborn"; Dr. Edward Clay Mitchell, Memphis, "Immunization"; and Dr. Horton Casparis, Nashville, "Tuberculosis in Childhood." The papers were followed by a round table discussion during the noon hour, at which time the speakers conducted a question box.

An effort was made to interest the general practitioner in child welfare by selecting topics of widespread application and well-qualified speakers. One hundred two attended the meetings, whereas only twenty-five men in the state limit their practice to pediatrics.

—A. C. Kirby.

Florida.—Members as of January 1, 1936	12
New members—1936	0
Applications pending	2
Total pediatricians in state	44
Number limiting their work	20

Organized activity of the Academy in Florida has definitely increased during the period since the last report of the regional chairman. Tangible evidence of this is offered in the development of the state pediatric society which held its inaugural session aboard the steamship "Florida" on April 27. Opposition to the formation of such an organization has heretofore been encountered. This year, sponsored by Academy members and meeting jointly with the state medical association, the pediatric program added materially to the interest of the general meeting. Many favorable comments have been heard from members who were not previously interested or acquainted with Academy activity. An effort was made to stimulate more general discussion in the subjects presented. This was patterned after the panel discussions of the national convention at Cleveland. After an appraisal of facilities for further development of maternal and child health programs, it was decided that the Academy in our state can best serve by cooperation with existing agencies and by an attempt to coordinate activities already begun. Immunization of the preschool child against diphtheria has been undertaken with the help of the Parent-Teachers' Association. Interesting figures are cited which indicate that this is a fertile field for intelligent effort. Diphtheria mortality per hundred thousand of population (South Atlantic States):

	1935	1934	1930-34	1925-29
Jacksonville	2.2	7.2	5.4	6.0
Miami	6.5	4.6	3.8	5.4
Tampa	6.6	2.8	4.8	4.6

One-third or more of the reported diphtheria deaths were among nonresidents. This is a grave factor among cities of our state where the tourist population represents a large percentage.

Academy members are cooperating with the state board of health in the promulgation of school health programs, as well as the routine examination of the school child. They also are serving as an advisory committee concerning problems peculiar to the children of specific localities.

The General Extension Division of the University of Florida conducts each year a graduate short course for doctors of medicine in the state. Recognizing pediatrics as one of the four basic fields of clinical medicine, the committee in charge devoted as much time on the program to pediatrics as to medicine and surgery. The Academy has been able to work in harmony with the state medical association in this excellent work which affords an opportunity for the doctors in rural sections and smaller towns to keep abreast with modern progress in medical science. Those who have lectured on pediatric subjects are prominently identified with the American Academy of Pediatrics. This short course of graduate instruction has been well attended.

Under the auspices of the Committee for the Study of Maternal and Infant Mortality, speakers have been provided for the education of nurses concerning pediatric nursing and technic. At Miami the Academy members were fortunate to have a meeting of the Jackson Memorial Staff devoted to this work with moving pictures illustrating the lecture.

Increased general interest in Academy activities is reflected in the growing membership in our state. At present most of the qualified pediatricians eligible for consideration are enrolled. The majority of the membership in Florida have expressed a preference for the type of regional meeting that will enable them to exchange ideas with their confreres by means of round table discussion groups. It is felt that the Academy program should add to the general interest in the Southern

Medical Association meeting. If possible, arrangement might be made to conduct the program of the Pediatric Section of the Southern Medical Association on the days immediately preceding or following the Academy meeting. This encourages the men to attend both meetings and keeps the expenditure both of time and money at a minimum. We still believe that active Academy membership should be extended only to those who limit their work to pediatrics.

—*Warren W. Quillian.*

Georgia.—Members as of January 1, 1936	16
New members—1936	1
Applications pending	1
Total pediatricians in state	87
Number limiting their work	43

At the meeting in July, attended by ten members of the Academy, the points brought out in your questionnaire were discussed. The men felt that the Pediatric Section of the Southern Medical Association and the regional meeting of the Academy should be held on the same day and not as we are holding them this year. As for the program, they were enthusiastic for a continuation of round table discussions and possible panel discussions.

The Academy in Georgia has worked in the main through the Georgia Pediatric Society. The activities of this organization are:

1. Business meeting in conjunction with the state meeting of the Medical Association of Georgia.
   Report of Committee on Postgraduate Education
   (Under the chairmanship of Dr. W. L. Funkhouser a postgraduate course for negroes was given at Emory University. The attendance was limited to twelve men. The schedule for this course is appended to this report.)
2. Scientific meeting.

The Georgia Child Health and Welfare Council has been active during the past year. This organization, sponsored by the Academy and other professional and lay groups, has already been described in detail.

The annual meeting was held in Atlanta on May 29. The chief purpose of the annual meeting is the discussion of important problems in the state and the crystallization of plans for activity throughout the state during the coming year.

A meeting of members of the Academy was held in Atlanta on July 10. The purpose of this meeting was to discuss various phases of the Social Security Act with which the Academy is concerned. Present to address the group were the director of the State Department of Health and the director of the Children's Division of the State Department of Public Welfare. These officials gave in some detail their plans for administering Title V of the act and requested the full cooperation of the Academy.

The status of that section of the act pertaining to the crippled child was discussed. The state will be unable to avail itself of these funds until the necessary legislation is obtained. The Academy is working in conjunction with the Department of Health and the Department of Welfare of the state and the WPA in an effort to study the problem of the crippled child and to present this in statistical form to the public and the legislature. In this way it is hoped to influence legislation favorably.

SCHEDULE OF PEDIATRIC CLINICS FOR NEGRO PHYSICIANS

July 13-17, 1936

Monday, July 13		
8:30 A.M.	Registration in senior lecture room, Grady Hospital.	
9:00 A.M.	Public Health	T. F. Abercrombie
10:00 A.M.	History and Physical Examination	M. H. Roberts
11:00 A.M. to 1:00 P.M.	Children's Ward—assigning patients and working up cases.	
2:00 P.M.	Out-Patient Service—Syphilis	Yampolsky and Kiser
4:00 P.M.	Infant Feeding	L. D. Hoppe
Tuesday, July 14		
8:30 A.M.	Surgical Conditions in Childhood	D. C. Elkin
9:30 A.M.	Well-Baby Clinic—Immunization	W. H. Kiser
11:00 A.M.	Ward Rounds	R. W. Dickson
12:00 Noon	Diarrhea	R. W. Dickson
2:00 P.M.	Clinical Laboratory	Jack Norris
4:00 P.M.	Tuberculosis	W. L. Funkhouser
Wednesday, July 15		
8:30 A.M.	Orthopedic Conditions in Infancy and Childhood	J. C. Sandison
9:30 A.M.	Ward Rounds	M. H. Roberts
11:00 A.M.	Urological Conditions in Childhood	M. K. Bailey
12:00 Noon	X-ray Examination as an Aid in Diagnosis of Diseases of Infancy and Childhood	J. J. Clark
2:00 P.M.	Out-Patient Service	Kiser and Dickson
4:00 P.M.	Newborn Infant	T. B. Gay
Thursday, July 16		
8:30 A.M.	Deficiency Diseases	
9:30 A.M.	Ward Rounds	T. F. Davenport
11:00 A.M.	Infectious Diseases	Lee Bivings
12:00 Noon	Upper Respiratory Diseases	R. G. McAliley
2:00 P.M.	Clinical Laboratory	Jack Norris
4:00 P.M.	Common Skin Diseases of Childhood	H. S. Alden
Friday, July 17		
8:30 A.M.	Surgical Conditions in Childhood	D. C. Elkin
9:30 A.M.	Ward Rounds	W. L. Funkhouser
11:00 A.M.	Prenatal Care	E. D. Colvin
12:00 Noon	Convulsions in Infancy and Childhood	T. F. Davenport
2:00 P.M.	Out-Patient Service	Roberts and Muse

—*M. Hines Roberts.*

Kentucky.—Members as of January 1, 1936	11
New members—1936	0
Applications pending	1
Total pediatricians in state	56
Number limiting their work	16

The decision of the members with regard to the questionnaire is that it is necessary to have both the annual and regional meetings. They get more out of the regional meeting, but the annual has to be held, and they like to have the opportunity of going in the fall or spring as it is more convenient for them. They would like to have more round table conferences but think that they should be limited to two hours each because under the present arrangement a man cannot attend more than two. Many times there are a number of subjects that a man would like to hear. They feel that the panel discussions are quite valuable but that there should be no more than two. They approve of having the two best pediatric papers presented; it seems to have met with success, and it stimulates a man to do his best writing that he may have the honor of presenting it at the pediatric meeting. They approve of having the meeting with the Southern Medical Association in the afternoon so as not to conflict with the Pediatric Section.

We have continued our postgraduate course of instruction in diseases of children, which has now been held for three years and is available to men within 100 to 150 miles of Louisville. We are also sending teams of two men to visit strategic points in the state to hold clinics, conferences, and public addresses to the laity on pediatric health subjects.

We have begun this year to hold a full day's pediatric meeting in conjunction with the state medical society. This will be held on the day before the meeting and will consist of a clinic, papers, and round table conferences. We have quite a good program to be presented and hope the meeting will meet with approval so that we can hold it each year. In addition, I have been able to arrange for a number of pediatric papers on the state medical program.

I have started a postgraduate course of work for the negro physicians in our city under the auspices of the department of pediatrics of the university. We will include in this course ward rounds and bedside work with the colored children in the City Hospital. In addition to this we are planning, in cooperation with the Maternal and Child Welfare Department of the State Health Department, work looking to a more extensive study and treatment of acute conditions in children.

—*Philip Barbour.*

Louisiana.—Members as of January 1, 1936	18
New members—1936	0
Applications pending	0
Total pediatricians in state	39
Number limiting their work	29

Many things have occurred in Louisiana since my last report, and there can be no denial that we are at the dawn of an era in medicine in New Orleans which indicates that the city is becoming a greater medical metropolis than it ever has been and that it is to take its place as a center of medical education second to none in the country.

With the dawn of this era in medicine as a whole in New Orleans, pediatricians will share liberally the increased opportunities which are about to be made available. Practically all of the buildings comprising the Charity Hospital, which have served for more than one hundred years and have created an atmosphere not unlike the old world hospitals, such as Guy's, St. Bartholomew's and Great Ormond Street in London, and Hôtel Dieu and Hôtel des Invalides in Paris, will be replaced with structures of a modern type, the central group being nineteen stories. At the present time the details of the pediatric facilities are too incomplete to discuss, but they will embody every feature which is now recognized as being desirable for pediatric care, from the period of the newborn to the twelfth year.

The organization of the services will be divided into three large divisions, and the requirements of the two medical schools, as well as the independent staff, are fully assured.

The Louisiana State Pediatric Society met with the state medical society in Lake Charles, La., April 27-29, 1936. The meeting was well attended by those confining their work to pediatrics as well as a large group of general practitioners especially interested in the subject. The program included papers and clinical case reports presented by Dr. Edwin A. Socola, Dr. Ruth G. Aleman, Dr. Philip C. deVerges, and Dr. Charles A. Bloom, New Orleans; Dr. Robert S. Lucas, Shreveport; Dr. J. A. Crawford, Lake Charles; and Dr. Cecil Lorio, Baton Rouge. Dr. Walter D. Brown, Beaumont, Texas, was the guest speaker and read his paper, "Use of Adult Blood in the Treatment of Pertussis."

For the ensuing year, the following officers were elected: president, Dr. Edwin A. Socola; vice president, Dr. Clarence H. Webb; and secretary-treasurer, Dr. Ruth G. Aleman.

The following pediatricians participated on the program of the Louisiana State Medical Society: Dr. Edwin A. Socola presented a paper in the Section on Public Health, which was discussed by Dr. Maud Loeber; and Dr. Rena Crawford, Dr. Emile Naef, and Dr. Don Julian Graubarth, New Orleans, presented papers in the Section on Diseases of Children, of which Dr. Robert A. Strong was chairman. Dr. Graubarth's paper was discussed by Dr. Ina M. Harper.

A postgraduate extension course in obstetrics was launched on October 5, under the sponsorship of the Louisiana State Medical Society, Committee on Maternal Welfare and Committee on Medical Education, and the Louisiana State Board of Health, Bureau of Parish Health Administration, and Division of Maternal Child Health. The meetings will be held for five consecutive nights for periods of two hours in cities centrally located in the congressional districts of the state. The course will consist of lectures, motion picture demonstrations, consultation conferences, and general discussions. A similar course in pediatrics is to be launched in the near future, and, while the details have not been worked out, they will probably be very similar to the course which was launched in Mississippi on July 6 under the auspices of the Mississippi State Medical Society, Board of Health, Tulane Graduate School and School of Medicine, Mississippi State Hospital Society, with the endorsement of the Mississippi State Pediatric Society.

In addition, the Louisiana State Pediatric Society proposes to hold a midwinter meeting besides its regular annual meeting. This meeting will be held in New Orleans and will be devoted largely to round table discussions of economic as well as scientific problems in pediatrics.

It is gratifying to note the awakening of interest in pediatrics which is illustrated by the keen desire for extension pediatric courses, not only in Louisiana, but in other southern states. There is evidence to indicate that this interest following so closely after the organization of the American Academy of Pediatrics, as well as the activities of Region II, is more than a coincidence. In short, I fully believe that there are unmistakable signs that the Academy and the regional activities are beginning to be far-reaching in their effect and that the organization has been completely justified.

—*Robert A. Strong.*

Mississippi.—Members as of January 1, 1936	6
New members—1936	0
Applications pending	1
Total pediatricians in state	27
Number limiting their work	12

I wish to report the following:

1. Every doctor doing pediatric work is now a member of the Academy, or his application is pending.
2. In response to a letter from Dr. M. Hines Roberts, a committee was appointed for Mississippi to serve on the Committee of Child Health Relations of the Academy.
3. A series of lectures constituting a postgraduate course in pediatrics was delivered by Dr. Robert A. Strong, of the medical department of Tulane University, in five different areas of the state; each course of lectures delivered daily for one week. These lectures were largely attended and were very beneficial and instructive. These lectures will probably be continued the early part of 1937. This work was done under the auspices of the state medical association, Mississippi Hospital Association, the state pediatric society, and Tulane University.

The members generally are very much impressed with round table and panel discussions. They do not express a particular choice, being satisfied with the discussion of any pediatric problems.

There is an opinion that if some central place were selected where satisfactory hotel accommodations could be had, it would be well to have the annual Academy meetings separate from the A. M. A. meetings, the regional meetings, when feasible, to be held in collaboration with sectional societies such as our region has held with the Southern Medical Association.

We think further that the plan to have the regional meeting following or preceding that of the S. M. A. and to alternate with the S. M. A. Section of Pediatrics, that is, when the section meets in the afternoon, let the Academy meet in the morning of the same day. I think that this plan, as far as the region is concerned, will meet with universal approval.

—*N. C. Womack.*

North Carolina.—Members as of January 1, 1936		17
	New members—1936	0
	Applications pending	1
	Total pediatricians in state	77
	Number limiting their work	31

I am giving a sketch of the work being done in North Carolina through the agency of the Social Security Act. The administration of the work for Maternal and Child Health Services, and also for crippled children, is being done by the state board of health, and that of delinquent children by the state board of charities under the direction of Mrs. Thomas Bost.

In formulating his plans for the maternal and child health work in the state, Dr. George M. Cooper, directly in charge, has sought the advice and consulted with a committee of twelve or fifteen pediatricians, obstetricians, general practitioners, and local health officers. I have had the pleasure of representing the American Academy of Pediatrics on the committee. A résumé of Dr. Cooper's progress is as follows:

Early this year, the United States Children's Bureau accepted the plan of joint operation of social security responsibilities, as proposed by the North Carolina State Board of Health. Also the United States Public Health Service approved the plans of the state board of health for this work. In both cases the funds had to be matched, that is, it had to be shown that the expenditures of the North Carolina State Board of Health from funds appropriated by the legislature and of

the various civil units of the state equaled the funds to be received from the United States treasury. The only exception to this is some money under what the Children's Bureau called "Fund B," which does not have to be matched.

The state board of health is receiving a little more than $300,000 from the public health service for the present fiscal year. This fund is expended through our county health department, a division of the state board of health. The state board of health is receiving from the Children's Bureau for maternal and child health service, including oral hygiene, about $137,000. The state board of health is also receiving for the fiscal year about $66,000, to be expended in work for crippled children.

The foregoing mentioned work is supervised and executed, and the fund dispensed, by the state board of health. The maternal and child health service, including the crippled children division and oral hygiene division, is expending its funds in the following manner: first, aid in the expansion of existing services for the benefit of women and children, particularly, and crippled children; and, second, in the establishment of health service for these groups in sections not already provided with any such service.

Dr. George M. Cooper is director of the maternal and child health service and also medical director of the crippled children's service; Dr. E. A. Branch, of the oral hygiene work; and Dr. R. E. Fox, of county health work. The secretary of the state board of health and the state health officer is Dr. Carl V. Reynolds. Under his general direction all of the work is organized.

So far this fiscal year, beginning July 1, special county nurses have already been placed in eleven counties not having any kind of whole-time service. Before the end of this month five more counties will be supplied with such service by the division of maternal and child health service. An additional nurse has also been provided for seven other whole-time health officer counties. This number will be increased to eleven before the end of the month. A total of about sixty maternity and infancy centers have either been established and are now under way or will be established during the next few weeks. In these centers prenatal service, postnatal service, and advice on infant care are offered to the poorer class of people. In cases in which confinement aid is needed, the nurses use their best endeavors to arrange with the welfare officer or other agencies for medical service or hospitalization at confinement.

The maternity and child health literature of the Children's Bureau, as well as that of the state board of health, is placed in the hands of each person reached through these centers. It is contemplated to have consultation service rendered to all mothers in these centers at frequent intervals by competent pediatricians. A practicing physician is in charge of each center one day in a month for the purpose of making the prenatal examination, etc.

It is too early yet to make a report on the progress made, but after the end of the first quarter, such a report will be compiled and will be available for any interested citizen.

At the summer meeting of the North Carolina Pediatric Society held at Roaring Gap, N. C., the members of the Academy felt that an annual meeting was preferable and like the innovation of having the two best pediatric papers presented at this meeting.

—*Aldert S. Root.*

Oklahoma.—Members as of January 1, 1936	14
New members—1936	0
Application pending	0
Total pediatricians in state	58
Number limiting their work	18

Pediatric activities in Oklahoma continue to move along with the members of the Academy carrying their share of the work. The center of interest in the state is the Oklahoma Pediatric Society which holds its annual meeting the first day of the meeting of the Oklahoma Medical Association. The 1936 meeting was held in Enid and was well attended by the pediatricians and those whose major interest is pediatrics.

The Oklahoma Society for Crippled Children continues to be very active. Clinics have been held in thirty-four different towns since January 1. A total of 1,008 children have been examined, and many of these have been referred to approved hospitals for treatment. Under the new law enacted by the last legislature, each county must make a special levy for the treatment of children whose parents are financially unable to provide the needed care. Any child who can be helped, or cured, may be committed to one of the 29 approved hospitals at the expense of his home county. County judges have committed 6,136 children under this law since the first of the year. This provides for all types of medical attention.

In May, 1935, Commissioner Collier called a meeting in his office to which he invited the members of the Children's Bureau staff to confer with him and members of his staff about cooperating with the Children's Bureau to meet the health and social needs of the Indian children. As a result of this conference, a committee was appointed consisting of Dr. Townsend, medical director of the Office of Indian Affairs, Dr. Estella Ford Warner, of the United States Public Health Service, Miss Lenroot, Dr. Martha Eliot, and Dr. Ethel Dunham. After a number of meetings for discussion of plans, it was decided to set up, in conjunction with the state health department, a complete health demonstration in Oklahoma as part of the state plan under Section 5 of the Social Security Act. The eastern section of Oklahoma was selected because of its rural area, one of great economic need, one in which little has been done from the health point of view, and one in which the population is largely Indian. The Children's Bureau has supplied a director of the maternal and child health program, Dr. Lewis K. Sweet, a pediatrician, who was appointed in April, 1936, selected by the Children's Bureau from the civil service list. A public health nurse, who will be educational director of maternal and child health, will be placed there soon. Child health conferences have been developed in the five counties (Mayes, Delaware, Cherokee, Adair, and Sequoyah) and a program of immunization against typhoid, diphtheria and smallpox is well under way. The cooperation of the local physicians has been obtained and the response to the program of the demonstration by Indian, negro, and white residents of the counties has been encouraging. It is hoped to develop complete welfare, nutrition, and dental services in the near future. Some research studies of the nutritional status of the Indian children will be made since malnutrition and deficiency disease are among the important problems in the area.

In the questionnaire sent to each member of the Academy in the state, most of the members expressed a preference for the annual rather than the regional meeting. All expressed approval of the innovation of having the best pediatric papers of the year presented. In most instances there was considerable disappointment expressed in the panel discussions. Something else in place of these would be preferred.

The round table discussions are more popular and the following subjects have been suggested for coming meetings: child psychology, allergy, rheumatism, dentistry, acute empyema, congenital syphilis, psychiatry, behavior problems, endocrinology, x-ray, the play school, parental psychology, child training, and pediatric teaching in the medical school. Some of these have been presented in the past but would be welcomed again. Most of the members do not approve of a joint

meeting with the Section of Pediatrics of the Southern Medical Association. There are many papers of interest in other sections that they would like to hear. The types of programs are different, and the Academy members are interested in more complete discussions and papers. The Oklahoma members, as a group, prefer that the meetings be kept apart as they have been in the past.

—*Clark H. Hall.*

South Carolina.—Members as of January 1, 1936	8
New members—1936	0
Applications pending	0
Total pediatricians in state	45
Number limiting their work	18

I wrote the letter in which I transmitted the questions that you sent me in a letter to twelve members, or prospective members, of the American Academy of Pediatrics. So far [Oct. 8, 1936], I have had no reply to my letter.

My personal opinion in regard to question 1 is that I am thoroughly satisfied with both the annual and regional meetings, especially when two regions can meet together. The round table discussions that I have attended seem to meet with much favor.

It is too late to suggest any answer to question 3. I think the two best pediatric papers of the year should be presented. The only difficulty is we might differ with the judges' opinion as to which are the two best papers.

I much prefer to have our meetings in conjunction with the Southern Medical Association and the American Medical Association, although it is bad that they should object to it. I do not feel that it hurts their meetings, because I feel that the men who do not stay to their section meetings would probably not take the trouble to go anyway and that a great many who would not attend their meetings would probably stay over because of the regional meetings. However, this might not be a correct diagnosis.

South Carolina under the Society Security Act adopted a plan which is a little different from the general plan adopted by other states. We decided to conduct prenatal and well-baby clinics, employing specialists to start the clinics and inviting the general practitioner to attend them in hopes that the attendance by the general practitioner would act in the place of the so-called refresher courses given by several of the states.

During the period of May to October, there have been held 160 well-baby clinics and 179 prenatal clinics, with the total attendance of 1,938 children and 1,132 pregnant women.

The attendance of general practitioners has not been very gratifying, but we feel encouraged and expect to continue our plan. After the general practitioner has attended a sufficient number of clinics, he is given the privilege of conducting said clinic, for which he is paid a reasonable compensation.

The crippled children's work is under the supervision of the state board of health, which has divided the state into five districts, a surgeon and a pediatrician being in charge of the clinics. A report of their work in detail is attached. Since the first of July, 937 patients have visited the clinics, and 174 have been hospitalized.

The American Academy of Pediatrics has not taken any active part in this work as a unit, but the individual members have done the work. Both of these above agencies have as chairman the state chairman, Dr. D. Lesesne Smith, Sr.

Total number well-baby clinics held	160
Total number prenatal clinics held	179
Total number of clinics held	339

	PRENATAL		WELL-BABY
May	38	20	18
June	49	24	25
July	47	24	23
August	55	29	26
September	66	36	30
October	84	46	38

Scheduled for November		93
Prenatal		50
Well-baby		43

Total attendance at prenatal clinics	1,132	White	397
		Colored	735
Total attendance at well-baby clinics	1,938	White	1,119
		Colored	819
Total number abnormalities—prenatal	1,752	White	605
		Colored	1,147
Total number abnormalities—well-baby	3,877	White	2,183
		Colored	1,694
Total number of prenatal patients with abnormalities	776	White	253
		Colored	523
Total number of children with abnormalities	1,493	White	810
		Colored	683

FIGURES TOTALED FROM CLINICS MAY-OCTOBER, INCLUSIVE
CRIPPLED CHILDREN

	DIST. 1	DIST. 2	DIST. 3	DIST. 4	TOTAL
No. clinic visits	312	298	243	84	937
No. patients visiting clinics	149	100	172	41	492
Cost of clinic	$ 245.50	$ 244.00	$ 84.00	$ 57.00	$ 630.50
No. of patients hospitalized	24	65	23	62	174
Cost of hospitalization	$ 869.35	$3,236.75	$3,314.25	$3,293.25	$10,713.60
Braces (number)	3	4	15	0	21
Cost of braces	$ 42.10	$ 198.00	$ 240.05	0	$ 480.15
Cost per patient hospitalized	$ 36.22	$ 49.86	$ 144.09	$ 53.12	$ 70.82
Cost per patient treated, hospitalized and treated	$ 6.74	$ 22.29	$ 13.53	$ 32.52	$ 18.77
Total amount spent	$1,166.95	$3,678.75	$3,638.30	$3,350.25	$11,824.25

—*D. Lesesne Smith.*

Tennessee.—Members as of January 1, 1936	22
New members	0
Applications pending	2
Total pediatricians in state	69
Number limiting their work	40

I have gone over the questions you asked with a number of pediatricians in the state who are members of the Academy, and as far as I have been able to learn those who have attended Academy meetings are satisfied with the arrangement that exists at present. They are more familiar with the regional meetings in association with the Southern Medical Association, since many of them have attended them. In talking with them, I have found no reason why the meeting time should not be alternated with the meetings of the S. M. A. on the same day. It seems to me

that no harm can come from trying that arrangement, for, if it is successful, it is barely possible that some similar arrangement can be worked out with the American Medical Association. At least, we cannot lose anything by trying it with the Southern Medical Association. In addition, the annual meeting seems to be necessary for a more general get-together, whether it becomes more closely associated with the American Medical Association or dissociated from it entirely.

In regard to question 2—a new subject seems to be of a good deal of interest—that of mental health. You will recall that round table in Kansas City was very large and the interest was great. It seems that allergy and infant nutrition are of sufficient interest to be maintained as round table subjects. Infant nutrition, of course, may cover normal nutrition or disturbed nutrition, or both. Immunizations might be continued for a while, but most pediatricians are so familiar with those subjects that the chief interest in that subject now lies with the general practitioners who have children to treat.

Those who attended the national meeting commented favorably on the presentation of the best pediatric papers during the year.

In regard to combining our meeting with the Pediatric Section of the Southern Medical Association—that was touched on in the beginning of this report. I personally feel that it is definitely worth while to try combining by alternating our Academy meetings with the section meetings on the same day.

Concerning the activities of the Academy in Tennessee—I have hesitated to attempt any organization of Academy members as an Academy function, and have preferred to exert our influence as Academy members through established channels because I feel that we can accomplish more if we can get our parents' organizations interested in better care of children. We have succeeded in getting a child health committee appointed as a subcommittee of the education committee of the state medical association. This committee is made up entirely of Academy members, and I have recommended that these individuals be appointed as state representatives of the Committee on Child Health Relations of the Academy and, at the request of Dr. M. Hines Roberts, that certain state representatives on this committee be appointed. I hereby recommend the following men for this committee:

Dr. William Anderson, Chattanooga; Dr. Hearn Bradley, Nashville; Dr. Oliver Hill, Knoxville; and Dr. Walker Rucks, Memphis.

As a step farther in the promotion of child health in Tennessee, Dr. John M. Saunders, who has had five years of training in pediatrics, has been appointed director of the Division of Maternity and Infant Hygiene of the Tennessee State Health Department. He is already outlining plans in cooperation with the educational committee of the state medical association and, under the direction of the state board of health, for reaching general practitioners and others who look after children. The final methods of this educational work are not completely worked out, but we have a set-up which will be conducive to progress in the promotion of child health. Dr. Saunders himself is a member of the Academy.

It should be recalled also that the chairman of our state board of health is a pediatrician. I believe he will soon be a member of the Academy. The medical schools are cooperating in every way possible with these groups in the promotion of child health, as well as carrying on post-graduate courses in pediatrics.

A further step in this direction is the development through the combined efforts of the State Health Department, the Tennessee Valley Authority, and the University of Tennessee, a course in health education for teachers. This health education is given at the University of Tennessee at Knoxville along modern lines and is to be extended as soon as possible to the normal schools of Tennessee.

In addition, individual members of the Academy are contributing to education through parent-teacher talks, medical society talks, and talks from various clubs.

In addition to all of this, a great deal of work is being done through the state health department and others actively interested in tuberculosis among children.

This report covers much but not all of the activity in the direction of better child health, and the work seems to offer prospect of good results if we as members of the Academy cooperate and actively use our influence in keeping it going.

—*Horton Casparis.*

Texas.—Members as of January 1, 1936	37
New members—1936	1
Applications pending	0
Total pediatricians in state	147
Number limiting their work	77

The Academy as a group has not sponsored any activity in the state this past year although the state chairman and other members inaugurated the work which has more recently been carried out through the state medical association and the Texas Pediatric Society in conjunction with the health department in the consummation of the functions of the Social Security Act. The state has been divided into sections governed by a councilor, and two-day refresher courses are being prepared to be given in three places in each district, a pediatrician and an obstetrician furnishing the program. The three pediatricians on the Committee on Maternal and Child Welfare of the association are Academy members, and the members of the Academy are in large part giving the courses.

Dr. Boyd Reading, Dr. C. O. Terrell, Dr. H. L. Moore, and Dr. Thomas J. McElhenney have been appointed as the committee to confer with the state health department. Dr. McElhenney is the chairman of the Child Welfare Committee of the American Legion for the state and has been very energetic in organizing their activities on a high plane.

Various members, including the state chairman, have carried out educational work both through groups and over the radio, always giving the Academy the publicity it deserves.

For May Day activities the state chairman offered the services of the Academy to the state health department and was assigned the duty of furnishing radio speakers for the various stations over the state. These speakers were furnished and did their work ably.

Invitations to join the Academy were sent to all pediatricians qualified to join but not yet members of the Academy.

Letters were sent to all members of the Academy, and follow-up letters were sent to those who did not respond to the first ones, in connection with the questionnaire sent out by the regional chairman. In response to the questionnaire sent out by Dr. Mitchell about twenty responses were received.

1. Most of the responses were in favor of both regional and annual meetings; two in favor of holding annual meetings only; and two, of regional meetings only. No suggestions were offered as to the nature of the meeting by most of those responding, although several suggested that the annual meeting devote considerable time to the discussion of medical economics as pertaining to pediatrics. A copy of one of the responses follows:

"I think the annual meeting should take up administrative matters and questions of policy. I have felt that some organizations, the Academy among them, are not aggressive enough in stemming the inroads made by public or semipublic agencies, such as boards of health and school boards. They have, of course, a proper function to perform, but in their zeal to make a good statistical showing their agents (nurses, etc.) frequently encroach upon the legitimate practice of the private physician in offering indiscriminately immunizations against communi-

cable disease. In a burst of enthusiastic altruism the Academy adopted a policy at the outset which, in my humble judgment, does not support and protect the best interests of its members in this important matter."

2. The opinions differ as to the subjects for round tables, but all apparently are in favor of their continuance. One suggested that the discussions be of clinical nature and not too theoretical. Subjects recommended for discussion follow: neonatal period, therapy, psychopathology and behavior problems, endocrinology, diarrhea, acute and chronic cold and respiratory infections, blood transfusion, allergy, and medical economics.

3. Panel discussions are satisfactory as they are at present with possible addition of the two subjects: nephrosis, and maternal infection and toxemia in the production of cerebral birth conditions.

4. The present system is satisfactory.

5. Most members favored alternating the meetings.

—*Edwin G. Schwarz.*

Virginia.—Members as of January 1, 1936	17
New members 1936	1
Applications pending	1
Total pediatricians in state	52
Number limiting their work	31

In regard to the questions raised in regional chairman's letter of June 24, I have written to, and talked to, the various members of the Academy in the state but have been able to get very little expression of opinion:

1. In general the men seem to approve of the present type of both annual and regional meetings.

2. The round tables meet with approval, but some members suggest that the leaders of these should be varied more than has been done in the past.

3. Panel discussions should be given about the same place on the program as previously.

4. Papers that have not been published should be of more interest.

5. The present plan of having the Academy sessions on the days preceding the meeting of the Pediatric Section of the Southern Medical Association is preferred to the plan of alternating morning and afternoon with this section.

There has been some criticism of the policy of having the Academy meeting place so far away from the headquarters of the Southern Medical Association on account of its lessening the opportunity for contacts with other men attending the meetings of the S. M. A.

The Academy in Virginia has continued to function through the activities of its members in other organizations in the state.

On May 29 the Virginia Pediatric Society inaugurated its new policy of holding a yearly clinical meeting to which the profession at large is invited. This year a morning session was devoted to a symposium, "Disorders of the Respiratory Tract in Infancy and Childhood," with papers presented by members of the society. This was followed by a paper, "Malignancy in Children" by Dr. A. C. Broders, clinical professor of pathology at the Medical College of Virginia. The afternoon was devoted to a clinical pathology conference conducted by a member of the department of pathology and the pediatric staff of the Medical College of Virginia.

In June, members of the Academy participated in the annual two-week St. Phillip Hospital Postgraduate Clinic for practicing colored physicians.

The department of clinical education of the medical society of Virginia has continued its activities in carrying postgraduate educational facilities to the phy-

sicians in various parts of the state. Dr. L. Shamburger has been engaged as a full-time clinician to carry on the postgraduate work in obstetrics, following the previous two and a half years' activity in this field by Dr. Maxwell E. Laphon.

It is also planned to continue the postgraduate courses in pediatrics that were begun two years ago. A full-time clinician, Dr. Jay Arena, has been engaged, who will give lectures and conduct clinics in various communities of the state in cooperation with the local medical societies. This postgraduate work is being carried on under a cooperative program of the Medical College of Virginia, the Department of Medicine of the University of Virginia, and the state department of health, all working under the general direction of the Medical Society of Virginia. The Extension Division of the University of Virginia acts as the executive agent. Members of the Academy are serving on the committees arranging for the above postgraduate activities.

A state committee to represent the national Child Health Relations Committee of the Academy has been appointed. This committee is composed of Dr. Charles E. Conrad, chairman, Dr. Lee E. Sutton, Jr., Dr. W. P. McDowell, and Dr. Samuel Newman. The state agencies administering the sections of the Social Security Act dealing with maternal and child health, crippled children, and child welfare, have been advised of the wish of this group to cooperate with them.

The Maternal and Child Health Services and Services for Crippled Children are under the administration of the state department of health; and the Child Welfare Services are under the state department of public welfare. Both the state health commissioner and the state commissioner of public welfare have welcomed the services of the Academy Committee and expressed a wish to have these representatives on their respective advisory committees when the meetings of the latter are called. With the state and federal funds that have been made available the above state departments are going ahead with a very progressive and constructive program. The Academy through its representatives should be able to render valuable service in cooperation with them.

—*J. B. Stone.*

West Virginia.—Members as of January 1, 1936	9
New members—1936	0
Applications pending	36
Total pediatricians in state	18
Number limiting their work	

I submitted the questions Dr. Mitchell included in his last letter to each member in the state and have had replies from several. The men like the type of round table discussions we have had and also the panel discussions. They all prefer an accurate transcript of the round tables. This seems to be the most popular section of the JOURNAL, and, while the method used this year may be just as accurate and a lot less expensive, the former method of having a stenographer take down everything seems preferable.

A good wholesome variety of round tables should be maintained. All of our men, being in the clinical field, prefer round tables on practical topics. This goes for the panel discussions also.

The presentation of the best pediatric papers of the year has been favorably reported upon.

Our members feel that friendly relations with the American Medical Association and the Southern Medical Association should be maintained but that the high quality of our annual and regional meetings should not be lowered.

The past summer witnessed the beginning of postgraduate education for rural physicians in West Virginia. Refresher courses lasting one week were held through-

out the state at convenient points so that every physician was in easy reach of one of these meetings. The topic for study this year was limited to Pediatrics, and the following members of the Academy served as instructors: Dr. George M. Lyon, Huntington; Dr. Raymond M. Sloan, Huntington; Dr. Andrew E. Amick, Charleston; Dr. J. L. Blanton, Fairmont; Dr. Charles W. Burhans, Cleveland, Ohio; and Dr. Lee Palmer, Louisville, Ky.

These refresher courses were well received throughout the state. The subject was handled in a practical manner, stressing particularly preventive pediatrics. Some of these meetings were held in the morning, some in the afternoon, and others in the evening. The evening meetings were much better attended. It is the desire of the West Virginia Medical Association and the West Virginia State Department of Health, the cooperating organizations sponsoring these courses, which are financed by funds from the Social Security Act, to conduct similar courses next year in obstetrics.

Numerous child health conferences were held during the late spring and early summer in various parts of the state. For the most part, these conferences were attended only by children entering school this fall. This means that the greater proportion of our immunizations are done at school age. However, efforts are being made to correct this situation, and in our lay education much stress is being given to early immunization against diphtheria and vaccination against smallpox.

During the annual meeting of the West Virginia Medical Association held in June, a dinner meeting of the Academy members was held. A frank discussion of various pediatric activities was freely participated in by all present, and a better understanding of our individual problems resulted. Dr. Lawrence T. Royster, University of Virginia, was our guest at this meeting. We hope to have similar meetings at least once a year.

—J. Lewis Blanton.

Academy News

The following men and women were elected to membership in the Academy:

Region II

Harvey F. Garrison, Jr., Jackson, Miss.
Isaac H. Grimball, Greenville, S. C.

Region III

Jennie Kantor Amtman, Chicago, Ill.
Roland E. Nutting, Duluth, Minn.
Meyer A. Perlstein, Chicago, Ill.
Charles L. Ruggles, Cleveland, Ohio
Norman C. Wetzel, Cleveland, Ohio

Region IV

Newell L. Moore, Santa Ana, Calif.
Jewyl Booth Murphy, San Mateo, Calif.
Lionel B. Saffro, San Pedro, Calif.

New appointments on the following committees were announced:

Committee on Clinical Investigation and Scientific Research—Dr. Wilburt C. Davison, Durham, N. C.; Dr. Francis Scott Smyth, San Francisco, Calif.; and Dr. Oscar Schloss, New York, N. Y.

Committee on Immunization Procedures—Dr. Horton Casparis, Nashville, Tenn.; and Dr. Charles F. McKhann, Boston, Mass.

Committee on Mental Hygiene—Dr. Bert I. Beverly, Chicago, Ill., chairman; Dr. C. A. Aldrich, Winnetka, Ill.; and Dr. Bronson Crothers, Boston, Mass.

Committee on Medical Education—Dr. Borden S. Veeder, St. Louis, Mo., chairman; Dr. C. A. Aldrich, Winnetka, Ill.; Dr. Henry F. Helmholz, Rochester, Minn. Subcommittee on Undergraduate Education—Dr. J. A. Johnston, Detroit, Mich., chairman; Dr. Alexis Hartmann, St. Louis, Mo.; Dr. Rustin McIntosh, New York, N. Y. Subcommittee on Postgraduate Education—Dr. George M. Lyon, Huntington, W. Va., chairman; Dr. Horton Casparis, Nashville, Tenn.; Dr. Hugh L. Dwyer, Kansas City, Mo.

News and Notes

The next meeting of the **Society for Pediatric Research** will be held at Chalfonte-Haddon Hall, Atlantic City, N. J., on May 4, 1937.

The following men and women have been certified by the **American Board of Pediatrics** since the last report:

John Bernard Ahouse, Yonkers, N. Y.
Morris Astrachan, Brooklyn, N. Y.
Hilde Bruch, New York, N. Y.
Frederick Castrovinci, New York, N. Y.
Stewart H. Clifford, Brookline, Mass.
Robert W. Culbert, New York, N. Y.
Charles S. Culotta, New Haven, Conn.
Katharine G. Dodge, New York, N. Y.
Elvira Goettsch, New York, N. Y.
Arthur Heyman, Newark, N. J.
Henry W. Kaessler, Bronxville, N. Y.
Jacob Kalish, Brooklyn, N. Y.
Morris Y. Krosnick, New Haven, Conn.
Milton Isra Levine, New York, N. Y.
Donovan James McCune, New York, N. Y.
Rosa Lee Nemir, New York, N. Y.
Antoinette Raia, Jackson Heights, N. Y.
Margaret Ruth Reynolds, Jackson Heights, N. Y.
Hyman Rubinstein, Brooklyn, N. Y.
Harry J. Seiff, New York, N. Y.
Abraham Tow, New York, N. Y.
H. Beril Warshall, Brooklyn, N. Y.
Paul G. Albrecht, Cleveland, Ohio.
Samuel A. Anderson, Jr., Richmond, Va.
Wm. Dulaney Anderson, Chattanooga, Tenn.
John Aull, Kansas City, Mo.
E. W. Barron, Columbia, S. C.
Frederic H. Bartlett, New York, N. Y.
Benjamin Bashinski, Macon, Ga.
Reuel A. Benson, New York, N. Y.
Joseph Vincent Bergin, Paterson, N. J.
Hugh Kling Berkley, Los Angeles, Calif.
Charles James Bloom, New Orleans, La.
David Hartin Boyd, Pittsburgh, Pa.
O. F. Bradford, Columbia, Mo.
Morris L. Bridgeman, Portland, Ore.
Alan Brown, Toronto, Canada
Charles R. Bugg, Raleigh, N. C.
Charles Wason Burhans, Lakewood, Ohio
Joseph Alexander Bybee, Beaumont, Texas
Randolph K. Byers, Boston, Mass.
Joseph K. Calvin, Chicago, Ill.
Walter Lester Carr, New York, N. Y.
Jerome Cochran Chapman, Birmingham, Ala.
Arch. B. Chappell, Middletown, N. Y.
Irving Claman, New York, N. Y.
George Becker Cornick, San Antonio, Texas
Howard Reid Craig, New York, N. Y.
Lyman Ray Critchfield, St. Paul, Minn.
William R. Cross, Knoxville, Tenn.
Jean Crump, Philadelphia, Pa.
George McClave Cultra, Amarillo, Texas
John C. Danahy, Cincinnati, Ohio
Daniel Cady Darrow, New Haven, Conn.
Tom Forest Davenport, Atlanta, Ga.
Ethel M. Davis, Chicago, Ill.
Roger William Dickson, Atlanta, Ga.
Henry Dietrich, Los Angeles, Calif.
Thomas Davis Dotterer, Columbia, S. C.
Hugh L. Dwyer, Kansas City, Mo.
Charles Judson Eldridge, Kansas City, Mo.
Lewis W. Elias, Asheville, N. C.
Henry C. Flood, Pittsburgh, Pa.
Arthur Petherick Foreman, Syracuse, N. Y.
Morgan Jacob Foster, Cedar Rapids, Iowa
Justin Allis Garvin, Cleveland, Ohio
Clain Fanning Gelston, San Francisco, Calif.
John Giblin, New York, N. Y.
Louie Oscar Godley, Fort Worth, Texas
Nathan Gorin, Boston, Mass.
Gaylord Willis Graves, New York, N. Y.
Berryman Green, Riverside, Calif.
Leonard H. Greenbaum, Los Angeles, Calif.
Joseph Greengard, Chicago, Ill.
Francis J. Gustina, Buffalo, N. Y.
Clark H. Hall, Oklahoma City, Okla.
John C. Hamilton, New York, N. Y.

Margaret I. Handy, Wilmington, Del.
Theodore Hudson Harrell, Mission, Tex.
L. P. Harsh, Akron, Ohio
Francis Bernard Hart, Brooklyn, N. Y.
Joyce I. Hartman, Cleveland, Ohio
Harold Herman, New York, N. Y.
Johanna Heumann, Chicago, Ill.
Miner C. Hill, New York, N. Y.
Russell R. Hippensteel, Indianapolis, Ind.
Gerald Norton Hoeffel, Boston, Mass.
Luther William Holloway, Jacksonville, Fla.
Elmer Grant Horton, Columbus, Ohio
Philip J. Howard, Detroit, Mich.
Henry Eugene Irish, Chicago, Ill.
Joseph Andrew Johnston, Detroit, Mich.
Basil Bradbury Jones, Richmond, Va.
Marion Yates Keith, Greensboro, N. C.
Dennis H. Kelly, Des Moines, Iowa
John M. Lee, Nashville, Tenn.
Edith M. Lincoln, New York, N. Y.
Harry R. Lohnes, Buffalo, N. Y.
Alexander Tertius Martin, New York, N. Y.
Charles Marcellus Mashburn, Atlanta, Ga.
W. Frederick Mayer, Johnstown, Pa.
Hugh McCulloch, St. Louis, Mo.
Kenneth M. Metcalf, New York, N. Y.
Edith M. Meyers, Oakland, Calif.
Myrl Milton Miller, Akron, Ohio
John McK. Mitchell, Rosemont, Pa.
Harold Ruckman Mixsell, New York, N. Y.
Cecile R. Moriarty, Minneapolis, Minn.
Edwin R. Murphy, Salt Lake City, Utah
Lewie H. Muse, Atlanta, Ga.
William S. O'Donnell, Detroit, Mich.
George F. Patterson, Cincinnati, Ohio
Jack Furman Perkins, Dallas, Texas
Giuseppe Previtali, New York, N. Y.
Harold W. Price, Calgary, Alberta, Canada
James Joseph Reilly, Camden, N. J.
George Renner, Jr., Cincinnati, Ohio
George Mathew Retan, Syracuse, N. Y.
Frank Howard Richardson, Black Mountain, N. C.
Fred Rittinger, Cleveland, Ohio
Worth Ross, Detroit, Mich.
Charles L. Ruggles, Cleveland, Ohio
Harold O. Ruh, Cleveland, Ohio
Robert Salinger, New Haven, Conn.
Arthur Saul Sandler, Chicago, Ill.
Saul Schlegman, White Plains, Ill.
Oscar M. Schloss, New York, N. Y.
John Ansel Schoonover, Denver, Colo.
Louis H. Segar, Indianapolis, Ind.
Frank Seinsheimer, Cincinnati, Ohio
Theodore King Selkirk, Cincinnati, Ohio
W. Ray Shannon, St. Paul, Minn.
Jeremiah T. Simonson, New York, N. Y.
John William Simpson, Birmingham, Ala.
William Ewing Sinclair, Orlando, Fla.
Raymond M. Sloan, Huntington, W. Va.
Charles Hendee Smith, New York, N. Y.
Arnold Miller Smythe, Des Moines, Iowa
Susan Page Souther, Hartford, Conn.
William St. Lawrence, New York, N. Y.
Walter Steoffler, Indianapolis, Ind.
Claudius A. Street, Winston-Salem, N. C.
Robert Alexander Strong, New Orleans, La.
William Walfred Swanson, Chicago, Ill.
Leo M. Taran, Brooklyn, N. Y.
Caleb O. Terrell, Fort Worth, Texas
Frederick Fitz Gerald Tisdall, Toronto, Canada
Joseph M. Ulrich, Akron, Ohio
Henry E. Utter, Providence, R. I.
Frank Van Schoick, Jackson, Mich.
Lynn B. Vaughan, Long Beach, Calif.
William Wirt Waddell, Jr., Charlottesville, Va.
Samuel Patrick Wainwright, Birmingham, Ala.
J. LaBruce Ward, Asheville, N. C.
Richard Gwyn Watson, Oakland, Calif.
Stewart H. Welch, Birmingham, Ala.
Stanley M. Wershof, New York, N. Y.
Theodore S. Wilder, Philadelphia, Pa.
Charles Alexander Wilson, Detroit, Mich.
Franklin Davis Wilson, Norfolk, Va.
John Armstead Winstead, Rocky Mount, N. C.
Alfred Maximilian Wise, Brooklyn, N. Y.
Ernst Wolff, San Francisco, Calif.
Bryon Parker York, Houston, Texas
James Herbert Young, Boston, Mass.
Paul J. Zentay, St. Louis, Mo.
Edmund R. McCluskey, Pittsburgh, Pa.
Ellsmer Landis Piper, Pittsburgh, Pa.

Book Review

Healthy Growth. By Martha Crumpton Hardy and Carolyn H. Hoefer, Chicago, 1936, University of Chicago Press.

"Healthy Growth" is only incidentally what its principal title implies—a study of growth changes in healthy children. It is primarily what its subtitle suggests—"A Study of the Influence of Health Education on Growth and Development of School Children." Four hundred nine children ranging in age from seven to twelve years at the time of enrollment were extensively studied from physical, psychologic, and educational points of view during a period of three years, the total study extending over a twelve-year period. The children were divided into three groups according to the amount of health education to which they were exposed. No details as to the nature of the health education afforded the experimental groups are given in this volume because the program has been previously reported, but this included special classroom instruction in addition to routine examinations and conferences with specialists. There is also no discussion of how the instruction given was supposed to bring about the results obtained. The authors have, however, called attention to possible indirect effects due to the influence of the whole program upon teacher, parent, and child attitudes and general school atmosphere and do not claim entire credit for the health content of instruction per se.

The body of the book is devoted to a presentation of the differences between the groups as discovered in the examinations and in the health and educational records. Significant statistical differences were found in favor of the experimental group in many of the items analyzed, while others showed little or no difference. The authors conclude that these studies present striking evidence of the influence of an efficient health education program on growth. Initial differences in the children composing the groups are frankly recognized and in some comparisons an attempt has been made to correct these by equating for the initial status. For example, 16 per cent of the experimental families spoke a foreign language as against 33 per cent of the controls, indicating underlying racial and cultural differences. The families of the experimental group had also enjoyed better educational opportunities and more economic and social advantages. It would seem that these differences might play a more important part in explaining the superior growth and educational progress of the experimental group than is credited to them in the authors' conclusions. Improvement recorded in health condition in both experimental and control children in some instances, as for example in posture, may well have represented the usual transition with advancing age from one type or stage of development to another, equally appropriate for the age in question but differing in relation to usual clinical standards of desirability.

The volume, however, represents a careful analysis and a thorough report of a vast amount of data of a type which is difficult to assemble, to control, and to interpret. The physician not particularly interested in health education programs will do well to turn immediately to the summary given in Chapter X to obtain the principal results of the study. Many of the earlier chapters will be found tedious in their statistical detail. Chapter XII will doubtless have more general interest because it compares the growth of children in "very good health" during the period of study with those in "fair health" and in "poor health." Positive correlations of varying degrees were found between the state of health, rate of growth, type of body build, intelligence, scholastic accomplishment, and behavior of these children. The volume will not prove very helpful to those who are primarily interested in the study of normal growth during the age period with which it deals.